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BRAIN TISSUE AMMONIA IN HUMAN SEPSIS-ASSOCIATED ENCEPHALOPATHY

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Recent studies have evidenced the significance of plasma ammonia level in incoming septic patients as an independent risk factor for short-term mortality along with the SOFA scale value [1]. Furthermore, plasma ammonia level was proposed as a novel laboratory biomarker of sepsis [2]. It is believed that hyperammonemia during sepsis is conditioned by multiple organ dysfunction syndrome including sepsis-associated liver injury (SALI) and acute liver dysfunction/failure [3, 4, 5]. Sepsis-associated encephalopathy (SAE) developing in response to systemic dysregulated inflammation accompanied by accumulation of DAMPs and PAMPs as well as diverse endotoxins, has highly complicated mechanisms [6]. The current study was addressed to detection of the histochemical level of ammonia in the brain tissue to clarify whether it correlates with the severity of neurogliavascular unit (NGVU) damage. Study was performed on the postmortem material patients died from abdominal sepsis with SAE according to SOFA score (n=35) – «SAE» group. 57.14% cases of «SAE» cohort had clinical features of SALI. We assessed histochemical (HC) ammonia level in the brain regions as follows: cerebral cortex, white matter, hippocampal dentate gyrus (DG), thalamus, striatum, and cerebellum using the method proposed by V. Gutiérrez-de-Juan et

al. [7]. Control group included postmortem brains of 30 patients died from acute heart failure. Ammonia-scale was based on assessing the optical density of HC-positive (orange/brown) precipitates expressed in conditional units of optical density (CUOD) at mag. x200 in ImageJ. CUOD values from 0 to 20 indicated negative («-») degree of ammonia expression; 21 to 50 CUOD mean weak («+») expression; 51 to 100 CUOD – moderate («++»); 101 and above CUOD – strong («+++») expression. The ammonia level in control group corresponded to negative expression. In the «SAE» group, tissue ammonia was increased compared to control: in the cortex – 2.89-fold (by 189.02 %), white matter – 1.95-fold (by 95.67%), hippocampal DG – 2.62-fold (by 162.37%), thalamus – 2.99-fold (by 199.48 %), striatum – 3.01-fold (by 201.41%), cerebellum – 2.87-fold (by 187.08%). Ammonia expression in the white matter and hippocampus assessed as weak («+»), while in the cortex, thalamus, striatum, and cerebellum – as moderate («++»). By these results we provide evidence that in the brain of deceased septic patients with SAE there is accumulation of tissue ammonia which can have a profound impact on the reactiveness of the NGVUs components and mechanisms of injury and tissue reparation. Considering the high percent of SALI cases in «SAE» group it might be supposed that high brain tissue ammonia in studied cohort is conditioned by sepsis-associated liver dysfunction/failure and addition of hepatotoxic impact on the brain. However, the growing body evidence underlines that during sepsis hyperammonemia can be of non-hepatic origin and these cases also appeared to be highly associated with incidence of SAE [8, 9].

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