


Chapter 13

Astroglia and Acute Hepatic Encephalopathy: The Mechanisms of Cytotoxic Brain Edema

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ABSTRACT

Acute hepatic encephalopathy (AHE) is a fatal neuro-psychological complication associated with acute liver failure (ALF). While different etiologies were established, over dosage of acetaminophen consumption is still the most frequent. The neuropathological basis of AHE induced death is still not fully understood; however, a body line of evidence sustains the role of rapid onset and progress of brain edema leading to intracranial hypertension, and finally brain herniation and death. The role of astrocytes in the pathogenesis of HE, in general, is well sustained through their role as a detoxifying component of the central nervous system, especially from peripheral generated ammonia, leading to astrocyte swelling, generally associated to brain edema onset. The current chapter will describe the pathomechanisms underlying astrocyte swelling in AHE, with the eventual evolution into macroscopic brain edema and the deathly herniation in humans as well as animal models of AHE.

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INTRODUCTION

Hepatic encephalopathy (HE) is a wide range of neuropsychiatric abnormalities resulted from impaired liver function (El-Mansoury et al. 2023; El Hiba et al. 2023; El Khiat et al. 2023). Acute liver failure (ALF) is defined as the pathological condition that refers to severe liver dysfunction which evolves rapidly leading to the onset of neurological complications commonly called acute hepatic encephalopathy (AHE), with very poor prognostic and which generally associated to high risk of coma and mortality, reaching up to 80%, while it represents approximately 0.1% of total death cases and 6% of liver related deaths. Otherwise, clinical observations in patients with ALF, support the presence of extended organs dysfunctions including kidneys, lungs, hearth and the circulatory system (Lee 2022).

AHE is well known as the common neuropsychiatric syndrome occurring in patients with ALF, which includes disturbances in consciousness, personality and intellectual capacity. Such neuro-clinical features are generally associated with severe biochemical abnormalities such as high blood ammonia levels, altered renal and hepatic markers, and peripheral inflammation.

The high mortality risk in AHE has been associated particularly to increased intracranial pressure (ICP) resulting in brain herniation. The pathophysiology of ICP may involve the development of brain edema which refers to excessive accumulation of fluid into the intracellular (cytotoxic edema) or extracellular (vasogenic edema) spaces of the brain parenchyma.

Particularly, cytotoxic edema involves astrocytic swelling, which is the most important histological hallmark observed in the brain tissue of patients with ALF (Kato et al. 1992) as well as in animal models of AHE (El Khiat et al. 2022a). While astrocyte swelling has been associated to several factors mainly ammonia, neuroinflammation and oxidative stress.

The clinical observation in patients with ALF sustains the evidence of a correlation between the severity of brain edema and blood and brain ammonia levels. While the establishment of such correlation has been confirmed in the *in vivo* and *in vitro* animal models of hyperammonemia (Norenberg et al. 2007).

The present chapter provides an updated overview of the pathophysiological mechanisms of astrocytic swelling underlying the development of cytotoxic brain edema in AHE, with special focus on the clinical observations and the experimental data.

BRAIN EDEMA: CLINICAL FEATURES

By definition, cerebral edema refers to increased amount of water within the brain tissue. Knowing that the brain bone is not extensible, water accumulation leads to progressive rise in the intracranial pressure (ICP), and therefore, the onset of intracranial hypertension (ICH). Such abnormality is generally associated to severe neurological complications due to decreased cerebral blood flow, tissue perfusion and ischemia (Larsen 1996).

ICH has been associated to acute forms of hepatic failures since the first description by Ware et al., in 1971 (Ware, D'Agostino, and Combes 1971). Such neurological complication was found in up to 80% patients with ALF at the coma stage (fig. 1, fig.2), while studies on animal models of ALF appeared to well mimic such clinical feature.

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