Abstract

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Pathophysiology of hepatic encephalopathy: review of the literature

Bologna C*, Donatiello I, Fontanella L, De Donato MT, Rabitti PG

Gastroenterology Unit, FADOI Campania, Naples, Italy

Hepatic encephalopathy (HE) is a serious complication of advanced liver disease and acute liver failure. It manifests itself with a wide spectrum of neuropsychiatric anomalies: from mild disorientation with disturbances of sensory and motor functions and cognition to coma and has a significant impact on the quality of life, morbidity and of patients, but also on caregivers and on re-hospitalization rate. Clinical severity, expressed in four degrees, ranges from moderate brain functional impairment (grade I) to coma (grade IV). The clinical presentation can be acute, characterized by episodes of short duration, or chronic with protracted and frequent episodes, apparently spontaneous (chronic recurrent) or with a subcontinuous neuropsychic impairment of moderate degree and not very sensitive to therapy (chronic permanent). The underlying alterations of hepatic encephalopathy are hepatocellular insufficiency and portosystemic shunts which, in the patient with cirrhosis, are present with varying degrees of association. Due to these alterations, substances of intestinal origin (ammonium, mercaptans, fatty acids, phenols, false neurotransmitters, substances with benzodiazepine-like action), not metabolized by the liver, pass into the systemic circulation, cross the blood-liquor barrier and induce a depression of the function of the central nervous system. Until the last decade there were three pathogenetic hypotheses formulated to explain the alterations of brain function in hepatic encephalopathy: the hypothesis of ammonium toxicity, that of an altered balance between excitatory and inhibitory neurotransmitters and, lastly, the hypothesis of a hyper tonus of the GABAergic inhibitory system. All are supported by clinical and experimental evidence; however none of them is conclusive or exclusive with respect to the others. In this review we will evaluate the latest pathogenetic hypotheses considered by the scientific community. HE is triggered by heterogeneous factors such as ammonia which is a major toxin, benzodiazepines, proinflammatory cytokines and hyponatremia. HE in patients with liver cirrhosis is triggered by low-grade cerebral edema and cerebral oxidative stress resulting in a number of functionally relevant alterations including post-translational protein modifications, RNA oxidation, gene expression alterations and senescence. It is suggested that these alterations impair the functions and communication of astrocytes. This involves the global slowing of brain activity, parallel to motor deficits and behavioural disturbances. It is now accepted that the intestinal environment is essential for the development of HE: the connection between microbes, inflammation and metabolic pathways in the pathogenesis of HE is becoming increasingly clear, providing exciting therapeutic perspectives.