Update in Hepatic Encephalopathy

In the forthcoming issues of the *Journal of Clinical and Experimental Hepatology*, the reader will find a series of articles that represent a consolidated effort at clarifying and simplifying our views on pathogenesis, classification and management of hepatic encephalopathy (HE). The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) organized 17th ISHEN Symposium that took place in Gurugram, India from 9 to 11 March 2017. Global experts convened for presenting their review of current literature on various aspects of HE, from nomenclature to etiology, pathogenesis, classification, diagnosis, treatment and to outcome. After an extensive discussion by the experts, the team have now compiled a series of review articles based on their research and clinical experience in this subject. Furthermore, these articles have been rigorously peer reviewed and compiled by the editorial board. A balanced opinion coming from different viewpoints of the experts is now presented as a *Special Section: Update in Hepatic Encephalopathy*.

The experts have discussed new insights in the pathogenesis of HE. Ochoa-Sanchez and Rose¹ discussed synergic interplay of pathological factors such as ammonia inflammation, oxidative stress,² bile acids,³ lactate,⁴ and extracellular glutamate and glutamatergic neurotransmission⁵ in the progression and severity of HE is emphasized. The synergic interaction between precipitating factors may better explain the progression and severity of HE in chronic liver disease. The review by Jayakumar and Norenberg⁶ summarizes the central role of ammonia in the pathogenesis of HE in human as well as in experimental models of acute and chronic liver failure.⁷ There is compelling evidence for a multifactorial causation in HE with factors like infections,⁸ reactive oxygen species,⁹ inflammatory cytokines,¹⁰ altered cerebral blood flow,¹¹ hyperthermia,¹² hyponatremia,¹³ lactic acid,¹⁴ neurosteroids,¹⁵ and more recently, the accumulation of cholesterol¹⁶ contributing to the pathogenesis. Azhari and Swain¹⁷ elaborate on the role of peripheral inflammation in the pathogenesis of HE. This article explores the new concept of periphery-to-brain communication pathways such as the gut–liver–brain axis as opposed to conventional pathways that involve neural networks¹⁸ and humoral (blood-borne) pathways, with increased circulating levels of endotoxin and cytokines, which activate cerebral endothelial cells and immune cells.¹⁹ Bjerring et al.²⁰ present a meta-analysis on the published data on cerebral blood flow (CBF) and metabolic rates from clinical studies of patients with HE. They provide

interesting conclusions from the analysis. Firstly, HE due to portacaval shunting (type B) was associated to an increased CBF, in contrast to studies of patients with HE of type A and C and secondly they found a cerebral accumulation of lactate due to hypoxic metabolism. Görg et al.²¹ comment on ammonia-induced senescence in astrocytes that involves glutamine synthesis-dependent formation of reactive oxygen species.²² They review the available data on premature senescence in astrocytes as a functional consequence of osmotic and oxidative stress in the pathogenesis of HE.²³ Finally, Butterworth et al.²⁴ present a systematic review and meta-analysis on the efficacy of L-ornithine L-aspartate (LOLA). They have concluded that LOLA was effective for improvement of mental state in all types of HE,²⁵ lowering of blood ammonia²⁶ and even the oral formulation was useful in minimal HE.²⁷

An enhanced understanding of the pathways that link the gut, liver and the brain in HE will allow for the development of targeted therapies to better manage the neurological, cognitive and behavioural complications of the liver disease. The Editors believe that the resulting compilation of reviews is informative and hope this appreciation will be shared by the reader.

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