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REVIEW

Hepatic encephalopathy: Sometimes more portal than hepatic

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Abstract

Hepatic encephalopathy is a severe complication of both chronic and acute liver diseases. The term hepatic encephalopathy stems from the belief that hepatic insufficiency is its fundamental etiopathogenic factor. However, most clinical cases show liver failure along with mesenteric venous portal hypertension. This portal hypertension would explain the abnormal mechanical forces suffered by the digestive tract in the early stages of the disorder. These forces could regulate some gut biochemical pathological pathways in a process known as mechanotransduction. Thus, portal hypertension would begin with the establishment of a mechanotransduced afferent or sensory inflammatory gut-brain pathway, resulting in functional and structural changes in the central nervous system. In this review, we will revisit the term "hepatic encephalopathy" in light of new results where portal hypertension occurs before liver failure and is accompanied by brain changes. Moreover, we will point out cellular links that can explain the microbiota, immune, gut, and brain axis disturbances found in this disorder.

Q5 Introduction

Hepatic encephalopathy (HE) is a severe complication of both chronic and acute liver diseases, and its pathogenesis has been poorly understood since the first neuropathological description of this complex disorder.[1]

In order to reconcile shortcomings and difficulties in accurately defining and classifying the severity of HE, in 1998, the World Organization of Gastroenterology introduced a multiaxial definition of HE[2] that included the precipitant factors, time-course, severity, and etiology. This classification was followed by the West Haven Criteria, which categorize HE into four stages based solely on clinical criteria.[3] Next, attempts such as the Hepatic Encephalopathy Scoring Algorithm[4] and the Clinical Hepatic Encephalopathy Staging Scale[5] were made to combine clinical and neuropsychological assessments in order to improve the grading sensitivity. Finally, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism proposed classifying HE Grade $\geq$ II as overt HE, whereas Grade 1 and mHE would be classified as covert HE.[6]

However, despite of these HE classification attempts,[7] less attention has been paid to its etiology. HE has been divided into three etiological types: type A, which is acute liver failure; type B, which includes portosystemic bypass without intrinsic liver disease; and type C, related to cirrhosis.[2] Regarding the HE etiopathogeny, there is no doubt about the independent roles played by liver failure[7,8] and gut-derived mediators,[9] which reveal the existence of a pathological gut-brain axis.

Indeed, the alteration in venous pressure in the mesenteric circulation appears to be the intestinal origin common to different types of liver failure.[10] In particular, most liver failure cases present mesenteric venous hypertension, such as portal, which is the reason the digestive tract prematurely experiences the effects of abnormal mechanical forces. Consequently, the incidence of pathological physical forces in the splenic venous territory could regulate the gut biochemical pathological pathways in a process known as mechanotransduction.[11]

This mechanical activation of cellular and subcellular inflammatory pathways in the gastrointestinal wall could be associated with the pathological stimulation of the vagal and spinal afferent endings, which may affect various brain structures. Therefore, portal hypertension will begin with the establishment of an afferent or sensory inflammatory gut-brain pathway resulting in functional and structural changes in the central nervous system, known as HE.

Understanding portal hypertension: Experimental development. Portal hypertension is characterized by increased pressure between the portal vein and the inferior vena cava. In turn, depending on the value of this portal pressure gradient, the severity of the portal hypertensive diagnosis varies.[10]

Another important factor is the level of portal hypertension obstruction, which has been classified as intrahepatic, post-hepatic, or pre-hepatic. The former is mainly caused by chronic liver disease, with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis, or non-alcoholic fatty liver disease. Therefore, in these patients, intrahepatic portal hypertension has been associated with the development of chronic

liver disease.[12] Post-hepatic obstruction is caused by thrombosis of the hepatic veins (Budd–Chiari syndrome), which is also associated with hepatocellular dysfunction.[13]

Finally, pre-hepatic obstruction, which could be caused by a blood clot in the portal vein, develops concomitantly with splenomegaly and portosystemic shunts. These patients have no underlying liver disease, and their liver function is expected to remain normal throughout life.[14] Hence, the pre-hepatic type has usually been chosen for the experimental study of portal hypertension because it involves less hepatic impairment. Particularly, the most frequently used experimental model of pre-hepatic portal hypertension employs partial portal vein ligation in the rat[15] or mouse.[16]

To develop this model, the rat or mouse is anesthetized, and after a laparotomy, the portal vein is dissected and isolated. In the mouse, a 25 to 27-gauge blunt-tipped needle is placed alongside the portal vein, and in the rat, a 20-gauge needle is used. A ligature is tied around the needle and the vein, and then the needle is immediately removed, yielding a calibrated stenosis of the portal vein.[17]

The intensity of the portal hypertension is determined by the resistance to the inflow produced by the constriction of the portal vein, conditioning its posterior evolution; therefore, this experimental model of pre-hepatic portal hypertension could be improved by increasing the initial resistance to the blood flow. Diez-Arias *et al.*[18] showed that by increasing the length of the stenosed portal tract with three equidistant stenosing ligatures, at the superior, medial, and inferior portions of the portal vein, respectively, when the position is maintained by the previous fixation of the ligatures to a sylastic guide, the splanchnic venous system pressure is equally increased. This procedure agrees with the Poiseuille equation ($R = 8\ \mu L/\pi\ r4$), where the resistance (R) to the flow of a vessel depends of the length (L), the radius (r), and the blood viscosity coefficient (μ). The stenoses are calibrated through simultaneous ligation with 3/0 silk around the portal vein in the rat and a 20-gauge needle in the mouse. Finally, two layers of the abdominal incision are closed.[17]

Thus, the degree of pre-hepatic portal hypertension and, consequently, mechanical splanchnic venous stress will increase more after triple partial portal vein ligation than after simple partial portal vein ligation. Therefore, with triple partial portal vein ligation, the increase in the mechanical stimuli will aggravate the biochemical response in the splanchnic veins, not only macroscopically, that is, splenic and mesenteric veins, but also microscopically, that is, post-capillary venules. In both cases, mechanical intravascular stress has a pathological effect on endothelial cells, which play a key role in initiating the inflammatory response.[19]

Mechanotransduction in pre-hepatic portal hypertension: A multiaxial impact. Consequences of the splanchnic endothelial inflammatory response to the mechanotransduction induced by portal stenosis could include large phenotypic macrovascular changes, such as portal-systemic collaterals formation[20,21] and mesenteric venous vasculopathy, that is, dilatation and tortuosity of the branches of the mesenteric veins[22] (Fig. 1). In addition, microscopic alterations can be observed, such as portal hypertensive enteropathy, characterized by an increased number and diameter of submucosal and mucosal vessels[23,24] (Fig. 2). F1 F2

At the same time, the phenomenon of endothelial mechanotransduction could include larger phenotypic cell-wide

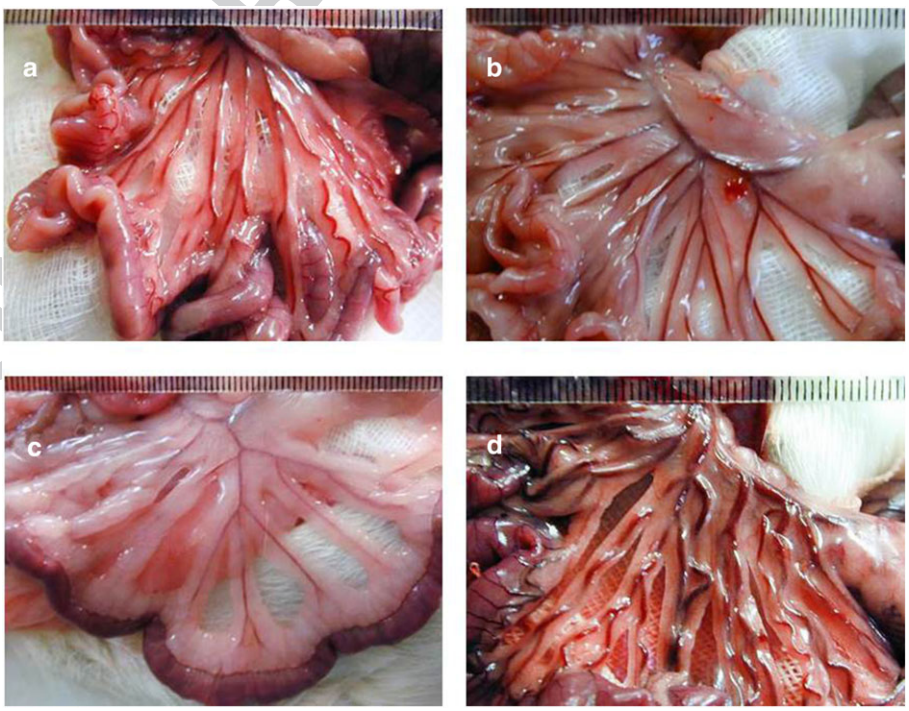

Figure 1 Mesenteric vasculopathy in normal and pre-hepatic portal hypertensive rat livers, where (a) and (b) indicate proximal and (c) and (d) distal mesenteric vasculopathy. [Color figure can be viewed at wileyonlinelibrary.com]

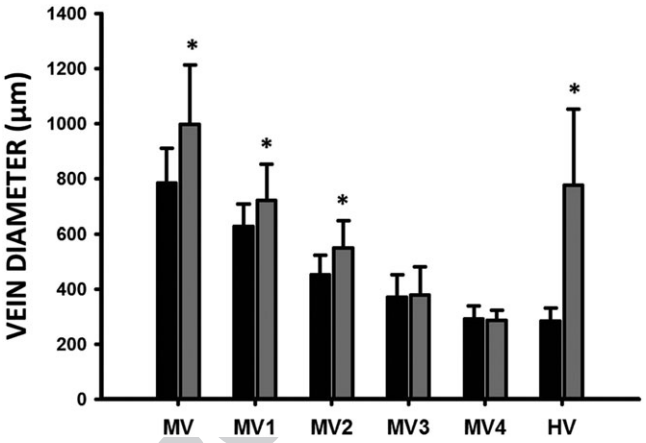

Figure 2 Diameter of the mesenteric veins (MV) and of first, second, third, and fourth orders, and of the hemorrhoidal vein (HV), in control and triple portal vein ligation animals 1 month after evolution. ▬, NC; ▬, PH.

changes occurring away from the site of the applied mechanical stress.[19] In particular, in the gastrointestinal tract, endothelial mechanotransduction ensures a rapid biochemical response of the nervous intrinsic afferents (enteric nervous system) and extrinsic afferents (vagal and spinal), which could initiate gut-brain neural reflexes (Fig. 3). F3

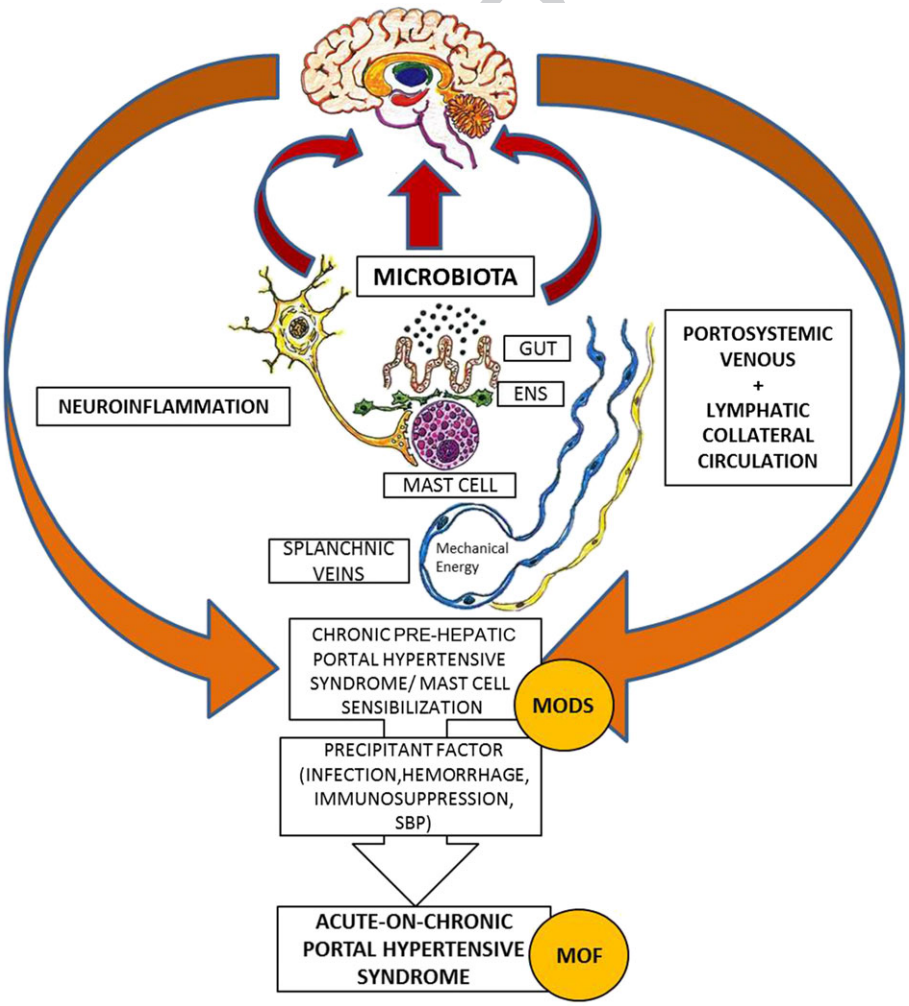

Figure 3 Schematic diagram of the mechanisms that produce portal hypertensive encephalopathy during the evolution of pre-hepatic portal hypertension. ENS, enteric nervous system; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure; SBP, spontaneous bacterial peritonitis. [Color figure can be viewed at wileyonlinelibrary.com]

Colour online, B&W in print

This gut-brain impact has been supported by Arias *et al.*,[25,26] who demonstrated that animals with pre-hepatic portal hypertension showed decreased metabolic brain consumption, along with lower density of astrocytes and an increase in the tumor necrotic factor-α in specific brain regions. Moreover, pre-hepatic portal hypertensive animals showed changes in the neuronal nuclear volume across the brain, underlying the cognitive deficits found in experimental models and patients.

Moreover, the activation of the gut-brain nervous axes could be supported by the activation of the gut-brain immune axis. Regarding this, it has been demonstrated that 1 month after portal hypertension, increases in fractalkine in mesenteric lymph nodes and its receptor in the small bowel and hippocampus are associated with an increased expression of the stromal cell-derived factor (SDF1α) in the hippocampus and cerebellum, and its respective receptor (CXCR4) in the small bowel, mesenteric lymph nodes, hippocampus, and cerebellum.[27] The impaired expression of chemotactic cytokines and their receptors in the splanchnic and brain areas studied suggests the existence of a gut-brain immune axis in portal hypertensive conditions where the development of endothelial splanchnic mechanotransduction could play an important role.

Furthermore, the phenotypic cell-wide changes secondary to gut endothelial mechanotransduction could also include changes in the gut microbiome. The intestinal microbiome is a densely populated microbial niche in the body, and there is growing evidence that it plays a key role in the regulation of brain function.[28] Disruption of the gut microbiota balance (dysbiosis) is known to contribute, among other things, to the pathogenesis of hepatic encephalopathy.[20,29] In fact, a growing body of evidence suggests that the microbiota-gut-brain axis could occur through various pathways, including the immune system, the vague nerve, the neuroendocrine pathway, and the portal and splanchnic lymphatic systems through bacteria-derived metabolites.[28]

The multifunctional mast cells have been proposed as an intermediary between these axes.[30] These immune cells have been shown to increase their number in the splanchnic area associated with pre-hepatic portal hypertension.[31] Their strategic location close to the blood vessels, nerves, and epithelium[30,32] makes them ideal candidates to orchestrate the harmful effects of the splanchnic intravenous increase in mechanical energy through the selective release of inflammatory mediators.[33] Therefore, mast cells would reinforce and integrate the joint activation of the immune, microbiota, gut, and brain axis (Fig. 2), and they could play a key role in linking intestinal immune signaling to the brain in portal hypertension. In addition, this cell population could migrate into the brain and induce and sustain neuroinflammation directly or through astrocytes, microglia, and neurons.[34]

This gut-brain relationship mediated by mast cells could explain the existence of splanchnic and systemic sensitization under pre-hepatic portal hypertension conditions that leads to multiorgan dysfunction syndrome. In this scenario, the presence of a second hit such as hemorrhage or infection will drive to multiple organ failure (Fig. 2).

Therefore, the pathological effects of intravenous splanchnic mechanical stress could be considered the main etiological factor in the production of HE through mechanotransduction in cases of pre-hepatic portal hypertension when there is no significant hepatic functional deficit.

For this reason, it is essential to allow the integration of mechanobiology in ongoing pathophysiological studies of hepatic encephalopathy. Through the investigation of the biomechanical activation of the gut-brain axis, the pathogenic origin of encephalopathy secondary to pre-hepatic portal hypertension could be established, suggesting that HE should be renamed portal hypertensive encephalopathy.[35] In particular, if portal hypertension precedes the onset of liver failure with clinical manifestations, it is possible that minimal HE would be a greater component of portal hypertensive encephalopathy than the HE itself. If so, knowledge about the neuropsychological characteristics of portal hypertensive encephalopathy during the progression of hepatic insufficiency would allow it to be differentiated from the neuropsychological characteristics of hepatic insufficiency.

Behavioral studies in rats with pre-hepatic portal hypertension revealed differential alterations compared with animals with portal hypertension associated with liver failure,[36,37] suggesting that the clinical features of portal hypertensive encephalopathy would facilitate its diagnosis and early treatment. Likewise, the early appearance of portal hypertension during the evolution of chronic liver diseases could allow them to be diagnosed early enough to be able to establish more effective therapies for hepatic insufficiency.

In conclusion, we should consider the hypothesis that pre-hepatic portal hypertension using the mechanism of mechanotransduction could stimulate the immune, microbiota, gut, and brain axis, which would be integrated by the mast cell function. This mechanism would explain the fact that precipitating factors of an explosive degranulated response of sensitized mast cells, that is, infection, hemorrhage, and/or hepatic dysfunction,[38] could cause an acute-on-chronic response during the evolution of portal hypertension. Likewise, other circumstances that lead to an increase in intra-abdominal pressure may be potential causes of increased venous pressure in the splanchnic venous system, as in obesity.[39] Therefore, they could also be factors in portal hypertensive encephalopathy. In light of this, we can hypothesize that the etiopathogeny of encephalopathy associated with pre-hepatic portal hypertension can be assessed through the biomechanical activation of the gut-brain axes, and so the term portal hypertensive encephalopathy should replace the term HE in early stages of liver disease.

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