Portal-systemic collaterals and hepatic encephalopathy

Chronic liver diseases or liver injuries commonly result in portal hypertension and the formation of portal-to-systemic collaterals (PSCs). PSCs form through the appearance of large or small vascular communications between the portal and systemic circulatory routes. These collateral vasculatures will shunt part of the portal blood flow, bypassing the liver, to the systemic circulation. Shunting the portal blood flow through collateral vessels is an attempt to decompress a highly pressurized portal system. However, the shunting of portal blood flow through PSCs may interfere with the detoxification processes of the liver. The uncleared toxic substances in the bloodstream may then reach the brain to cause neurological dysfunction, known as hepatic encephalopathy.

Hepatic encephalopathy is an important complication occurring in severe acute or chronic liver injury. At present, the pathophysiology of hepatic encephalopathy is not completely understood. Recent evidence has shown that hepatic encephalopathy is a multifactorial and complex disease involving the imbalanced production, metabolism and regulation of various neurotransmitters. However, it is generally accepted that ammonia is a key molecule, playing an important role in the pathogenesis of hepatic encephalopathy. Under normal conditions, the ammonia generated by enterocytes and bacteria in the colon will be transported by the portal vein to hepatocytes for detoxification. However, in the injured liver, hyperammonemia may occur, either through the overproduction of ammonia in the intestine or due to a reduction in the metabolic capacity of the liver’s urea cycle. The clearance of ammonia may be compromised further by the presence of portal-systemic shunting. Therefore, understanding the role of PSCs in the pathophysiology of hepatic encephalopathy is a practical and important issue.

The Working Group on Hepatic Encephalopathy has published the classification of hepatic encephalopathy according to its clinical presentation and etiology. Hepatic encephalopathy can be divided into three categories: Type A, acute liver failure; Type B, a portal-systemic bypass without intrinsic liver disease; and Type C, cirrhosis with portal hypertension and/or a portal-systemic shunt. Type C can be further divided into three patterns, the episodic, persistent, and minimal hepatic encephalopathy, depending on the clinical presentation of the patient. Patients suffering from episodic hepatic encephalopathy may have seemingly normal cognitive functioning between episodes. Patients with persistent hepatic encephalopathy never become completely free of hepatic encephalopathy. Patients with minimal hepatic encephalopathy remain clinically undetectable.

Portal-systemic shunting is the major cause in patients with Type B hepatic encephalopathy. This type of encephalopathy was first described as “portal-systemic encephalopathy” by Raskin et al in 1964. The main feature of these patients is that liver injury and portal hypertension may be slight or absent in them. For this reason, patients with Type B hepatic encephalopathy are frequently misdiagnosed as having psychiatric disorders such as dementia, depression and others. The actual cause of the formation of PSCs in these patients remains unclear; possible etiologies include congenital abnormalities and degenerative changes, or they may be secondary to invasive procedures or trauma. Based on the location of shunting, either inside or outside the liver, Watanabe et al classified this disease into five types and suggested appropriate treatments. It is worth noting that portal-systemic encephalopathy has been increasingly reported in the literature in recent years.

It is crucial to have an appropriate animal model to study the pathophysiology of hepatic encephalopathy and to test potential therapies. Although there are several animal models for the study of liver disease, a satisfactory animal model of hepatic encephalopathy is still lacking. Portacaval anastomosis (PCA) in rats is the most used animal model in the study of chronic hepatic encephalopathy. An end-to-side PCA creates 100% portal-to-systemic shunting but, however, it lacks hepatocellular injury. The hyperammonemia model is created by feeding animals with an ammonium acetate-supplemented diet, with urea or by an injection of ammonium. It is a useful model to study the toxic effect of ammonia and related metabolic changes, but there is no liver injury or portal-systemic shunting in this model. The chronic liver-injured model of hepatic encephalopathy can be induced by common bile duct ligation (CBDL). In this model, the amount of portal-systemic shunting develops gradually but varies widely from less than 30% up to 60%. Though CBDL rats may not develop overt hepatic encephalopathy, their ammonia levels are increased and their motor activities are decreased. Thioacetamide-induced fulminant hepatic failure has also been used in the study of hepatic encephalopathy. In addition to severe liver injury, this model presents with neurological
and cognitive dysfunctions and without significant portal-systemic shunting. Recently, the partial portal vein ligation (PVL) model was used to investigate the role of PSCs in the development of hepatic encephalopathy by Hsin et al.\textsuperscript{13} In the PVL model, liver function is completely normal and the degree of portal-systemic shunting is usually greater than 90\%. The PVL model is similar to the PCA model, with only small differences in the degree of portal-systemic shunting. These two animal models represent models of Type B hepatic encephalopathy.

The study of Hsin et al found that high-degree portal-systemic shunting without significant liver damage in PVL rats may not be adequate for the development of hepatic encephalopathy.\textsuperscript{13} This observation is not fully consistent with the clinical presentations of patients with Type B hepatic encephalopathy. It is possible that the neuropsychiatric presentations of Type B hepatic encephalopathy cannot be reproduced in the PVL model or are undetectable by current methodology. Moreover, the measurement of motor activities may not be sensitive enough to detect the subtle neuropsychiatric changes in Type B hepatic encephalopathy. In contrast, Hsin et al found that there was a significant correlation between the degree of portal-systemic shunting and the changes of motor activities in CBDL rats (a model of Type C hepatic encephalopathy). Thus, it is reasonable to say that liver function impairment is more critical for the development of hepatic encephalopathy compared with PSCs. However, when liver dysfunction is not significant, the PSCs themselves may become the major cause of Type B hepatic encephalopathy, delaying the clearance of circulating neurotoxins and precipitating or sustaining neuropsychiatric dysfunction. The relationship among hepatic detoxification ability, neurotoxins and the degree of portal-systemic shunting in the pathophysiology of portal-systemic encephalopathy deserves further investigation in future study.

Currently, there is no good model of hepatic encephalopathy suitable for all purposes of studies. The ideal animal model of hepatic encephalopathy should have chronic liver injury, PSCs, wide-range presentation of hepatic encephalopathy from subclinical to deep coma, precipitation factors and characteristic brain changes.\textsuperscript{11} With this ideal model, the interplay between PSCs and other neurotoxic factors and the complex pathogenesis of hepatic encephalopathy may be gradually revealed.

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References