Review

Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure

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Summary

Hepatic encephalopathy in a hospitalized cirrhotic patient is associated with a high mortality rate and its presence adds further to the mortality of patients with acute-on-chronic liver failure (ACLF). The exact pathophysiological mechanisms of HE in this group of patients are unclear but hyperammonemia, systemic inflammation (including sepsis, bacterial translocation, and insulin resistance) and oxidative stress, modulated by glutaminase gene alteration, remain as key factors. Moreover, alcohol misuse, hyponatremia, renal insufficiency, and microbiota are actively explored. HE diagnosis requires exclusion of other causes of neurological, metabolic and psychiatric dysfunction. Hospitalization in the ICU should be considered in every patient with overt HE, but particularly if this is associated with ACLF. Precipitating factors should be identified and treated as required. Evidence-based specific management options are limited to bowel cleansing and non-absorbable antibiotics. Ammonia lowering drugs, such as glycerol phenylbutyrate and ornithine phenylacetate show promise but are still in clinical trials. Albumin dialysis may be useful in refractory cases. Antibiotics, prebiotics, and treatment of diabetes reduce systemic inflammation. Where possible and not contraindicated, large portal-systemic shunts may be embolized but liver transplantation is the most definitive step in the management of HE in this setting. HE in patients with ACLF appears to be clinically and pathophysiologically distinct from that of acute decompensation and requires further studies and characterization.

Keywords: Hepatic encephalopathy; Ammonia; Systemic inflammatory response; Glutaminase; Bacterial translocation; Diabetes mellitus; Microsatellite.
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Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; HE, hepatic encephalopathy; GLS, glutaminase; ROS, reactive oxygen species; IL, interleukin; TNF, tumour necrosis factor; BT, bacterial translocation; SIBO, small intestinal bacterial overgrowth; DM, diabetes mellitus; IR, insulin resistance; COX, cyclooxygenase; OTC, ornithine transcarbamylase; OPE, ornithine-phenylacetate; LOLA, L-ornithine L-aspartate.

Introduction

Hepatic encephalopathy (HE) is a major complication of liver cirrhosis, affecting up to one third of cirrhotic patients and is classified into three types: Type A HE is due to acute liver failure (ALF); type B HE is due to portal-systemic shunting without intrinsic liver disease; and type C HE occurs in patients with underlying cirrhosis [1]. HE manifests as a spectrum, ranging from minimal disturbances in mental function that impact on attention, cognition and quality of life to coma. In this review, patients with type C HE who require hospital admission will be discussed.

Using the Clinical Practice Research Datalink in the UK, the presence of HE in hospitalized cirrhotics was associated with significantly higher mortality [2]. In the USA, between 2005 and 2009, the incidence of new patients hospitalized due to hepatic encephalopathy slightly increased and showed more severe disease, expanding resource utilization and keeping mortality stable [3]. Recent prospective studies, evaluating the natural history of hospitalized cirrhotic patients, have started to provide new information about the prevalence and outcome of HE [4]. Of the 1348 patients studied, 460 had varying grades of HE (34%): 43% died within 1-year and the short-term mortality rate was significantly higher in patients with more advanced grades of HE. The subgroup of patients with high short-term mortality and organ failures had a higher mortality. This patient group was referred to as acute-on-chronic liver failure (ACLF) [5]. An important new concept that has emerged is that the presence of HE with or without ACLF is associated with a significantly worse outcome compared with non-HE patients [6]. The data indicate that HE independently of other organ failures adds significantly to the risk of death (Fig. 1). Moreover, in a prospective cohort from NACSELD (North American Consortium for study of end-stage liver disease), including 507 hospitalized decompensated infected cirrhosis patients, hepatic encephalopathy grade 3/4 was the most commonly detected organ failure and the number of organs influenced survival [7].

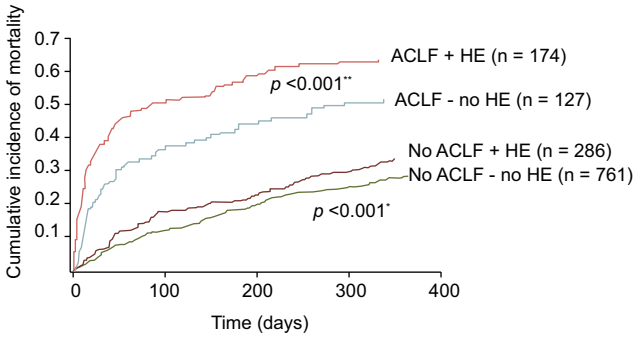

Fig. 1. Actuarial survival curve of hospitalized cirrhotic patients showing mortality of patients with or without ACLF in combination of with or without overt hepatic encephalopathy. Mortality rate was significantly higher in patients with ACLF and HE in comparison with non-HE patients with ACLF. In decompensated cirrhosis HE was also related to a raised mortality. Adapted from Cordoba J. *et al.* [6].

Key Points

- Interorgan ammonia trafficking, systemic inflammation and oxidative stress, modulated by glutaminase gene alteration, are key factors in the pathophysiology of hepatic encephalopathy (HE)
- HE in acute-on-chronic liver failure (ACLF) patients is distinct clinically, prognostically and pathophysiologically to the conventional forms represented in type A, B and C of HE
- Management of HE in hospitalized patients requires admission to the ICU when the Glasgow Coma scale is less than 8. Precipitating factors should be identified and treated. Specific measures should be focused on decreasing hyperammonemia and systemic inflammatory response. Albumin dialysis and embolization of portosystemic shunts could rescue refractory patients
- Hepatic encephalopathy in critically ill, hospitalized cirrhotic patients should be considered a high priority criteria for liver transplantation. However, at present there is no priority for severe HE patients on the waiting list

Pathophysiology of hepatic encephalopathy in hospitalized patients

The pathophysiology of HE is multifactorial and complex but hyperammonemia, systemic inflammation and genetic factors are thought to be important. There are no human neuropathologic data but electron microscopic studies in animal models of ACLF show that the astrocytes are swollen with markedly vasoconstricted blood vessels [8]. Increased intracranial pressure is common in patients with ALF. In patients with ACLF, an overt increase in intracranial pressure and cerebral oedema-related deaths have been described in small case series [9,10]. More recently, a retrospective study suggested that overt cerebral oedema was observed in about 5% patients with ACLF [11], which was confirmed by imaging studies [12]. Therefore, although brain swelling is a feature of ACLF, the relatively low incidence of deaths from cerebral herniation may be related to cerebral atrophy or reduced cerebral perfusion, which are known features of cirrhosis and HE [13].

Hyperammonemia

In the brain, astrocytes are the only cells that metabolize ammonia by the enzyme glutamine synthetase, converting glutamate and ammonia into glutamine. Glutamine accumulation, as an osmolyte, promotes astrocyte swelling [14]. Ammonia also induces oxidative, cellular stress and energy failure.

Data regarding a direct correlation between ammonia concentration and the severity of HE are limited. In a systematic review, a general correlation between higher levels of ammonia and more severe encephalopathy in cirrhosis was observed [15]. More recently, a retrospective study in cirrhotic patients with grade 3/4 HE showed that patients were hyperammonemic but the absolute levels did not correlate with the severity of HE [16]. Studies in animal models have consistently shown that induction of hyperammonemia results in brain oedema and the reduction in ammonia translates into reduced brain swelling, firmly confirming the central role of ammonia as a therapeutic target [16]. Interestingly, in a model of cirrhosis, reduction in ammonia concentration protected the brain from a subsequent challenge with lipopolysaccharide [17]. Thus, ammonia seems to sensitize the brain to a secondary inflammatory insult.

Inflammation

Inflammatory response, infections and sepsis

The impact of the systemic inflammatory response on ammonia-induced brain dysfunction was described in cirrhotic patients admitted to the hospital with infection [18]. The main source of inflammation in cirrhotics was infection and sepsis. Ammonia-induced deterioration in neuropsychological dysfunction was prevented by antibiotics, supporting the notion of a synergy between ammonia and inflammation in the pathogenesis of HE. Merli *et al.* confirmed the presence of cognitive impairment (overt or subclinical) in 42% of cirrhotics without infection, in 79% with infection and in 90% with sepsis [19]. Hung *et al.* observed that infections increase the mortality of HE cirrhotic patients, especially pneumonia and sepsis without specific focus [20]. Lastly, in the CANONIC study described above, a clear role for systemic inflammation was demonstrated in patients with advanced HE, which correlated with mortality.

Neuroinflammation, hyponatremia and oxidative stress

Changes in the permeability of the blood-brain barrier (BBB) to water and other small molecules [21,22] together with hyponatremia [23] and oxidative stress have been implicated in HE [24]. The BBB protects from common bacterial infections or toxins, and from the fluctuation of plasma components and neurotransmitters in the blood. During infection, microglial cells (the resident macrophages of the brain) and astrocytes may release pro-inflammatory cytokines (TNFα, IL-6), which enhance neuropsychological impairment induced by hyperammonemia [25] but this observation remains controversial [26,27]. Nonetheless, TNFα levels correlate with HE severity [28] and some anti-TNFα drugs like etanercept and infliximab work on animal models of HE. Moreover, COX-1 inhibitors and NSAIDs have been found to