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REVIEW ARTICLE

Hepatic encephalopathy in acute-on-chronic liver failure

Guan-Huei Lee[1]

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Abstract The presence of hepatic encephalopathy (HE) within 4 weeks is part of the criteria for defining acute-on-chronic liver failure (ACLF). The pathophysiology of HE is complex, and hyperammonemia and cerebral hemodynamic dysfunction appear to be central in the pathogenesis of encephalopathy. Recent data also suggest that inflammatory mediators may have a significant role in modulating the cerebral effect of ammonia. Multiple prospective and retrospective studies have shown that hepatic encephalopathy in ACLF patients is associated with higher mortality, especially in those with grade III–IV encephalopathy, similar to that of acute liver failure (ALF). Although significant cerebral edema detected by CT in ACLF patients appeared to be less common, specialized MRI imaging was able to detect cerebral edema even in low grade HE. Ammonia-focused therapy constitutes the basis of current therapy, as in the treatment of ALF. Emerging treatment strategies focusing on modulating the gut-liver-circulation-brain axis are discussed.

Keywords Hepatic encephalopathy · Acute-on-chronic liver failure · Cerebral edema · Brain imaging

Introduction

Disturbances of brain function are common in patients with acute-on-chronic liver failure (ACLF) [1]. The most frequent manifestation is hepatic encephalopathy. In cirrhosis, the development of hepatic encephalopathy is related to precipitating factors that increase the exposure of the brain to toxins. In patients with ACLF, additional aspects of major pathophysiological importance are the systemic inflammatory response, circulatory dysfunction and failure of other organs that can directly cause brain function disturbances. This article reviews the recent findings in the pathogenesis of hepatic encephalopathy and focuses on its importance in prognosticating the outcome of ACLF.

Pathophysiology

Hepatic encephalopathy is a common manifestation of ACLF. Local and systemic changes have been implicated in the pathophysiology of the development of this neurological syndrome. Recent further analysis of the CANONIC cohort has provided additional insights into the pathogenesis of HE associated with ACLF, which occurs predominantly in younger patients with severe liver failure and systemic inflammatory response [2].

From the pathophysiological perspective, brain edema is an important feature of ACLF. As the syndrome occurs against the background of existing cirrhosis and chronic portacaval shunting, a degree of brain atrophy protects from this brain swelling, resulting in an increase in intracranial pressure. MRI studies showed that cerebral edema developed in ACLF, but usually to a lesser extent than in acute liver failure [3]. An increase in brain swelling can be reversed with liver transplantation supporting the notion that, like acute liver failure, the brain manifestation of ACLF is a reversible disorder.

Ammonia levels, systemic inflammation/SIRS and cerebral hemodynamics all appear important and have been well described in ALF and cirrhosis, but their relative roles

✉ Guan-Huei Lee
guan_huei_lee@nuhs.edu.sg; mdcleegh@nus.edu.sg

[1] Department of Medicine, National University Health System, 1E, Kent Ridge Road, Singapore 119228, Singapore

in ACLF have not been elucidated [4, 5]. The central role of ammonia in the development of HE has been well described in both animal studies and human subjects [5, 6]. The accumulation of water is located in the astrocytes and is related to the effects of ammonia, which is metabolized into glutamine. It has been proposed that the transport of glutamine into the mitochondria yields high levels of ammonia inside the mitochondria and induces oxidative stress.

Against the background of this hyperammonemia, an added hepatic insult and/or superimposed inflammation leads to the development of brain edema, suggesting a synergy between ammonia and inflammation. This was demonstrated in an animal model of ACLF, where cirrhotic rats administered endotoxin mimic the experience of clinical patients with ACLF who developed brain edema [7]. Activation of microglia and induction of inflammation within the brain in the rat hepatic encephalopathy model has been observed, which may contribute to brain dysfunction [8].

Hyponatremia, a common finding in ACLF, may exacerbate astrocyte swelling because of differences in osmolality between the intra- and the extracellular compartments [9, 10]. The enhancement of brain edema may be the explanation for why hyponatremia is the most important risk factor for the development of hepatic encephalopathy among patients with advanced cirrhosis. An additional factor that may have a role in the development of brain edema in ACLF is an increase in blood-brain barrier permeability. A possible explanation is disruption of tight-junction proteins in brain endothelial cells caused by the effect of inflammatory mediators activated in ACLF [11].

Cerebral blood flow is known to be progressively reduced in cirrhosis but in ACLF may be paradoxically increased as seen in patients with acute liver failure [4]. In a recent study, the acute effect of insertion of a transjugular intrahepatic shunt, which is known to induce endotoxemia, was studied in patients with cirrhosis. The study demonstrated that TIPSS-induced endotoxemia led to an increase in the rate of production of nitric oxide, which was associated with endothelial dysfunction and increased cerebral blood flow supporting the hypothesis that multiple hits and brain swelling are features of ACLF [12].

Does the grade of hepatic encephalopathy influence survival?

The most important factor that determines prognosis in patients with ACLF and hepatic encephalopathy is the development of multiorgan failure. Scoring systems that have been developed for critically ill patients (Acute Physiology and Chronic Health Enquiry—APACHE II and

Table 1 The characteristics of studies investigating hepatic encephalopathy as a prognostic factor for acute-on-chronic liver failure

Ref.	Materials/methods (no. of patients), age, uni-/multi-a., kind of study	Etiology (no. of patients)
Garg et al. [14], India	27 patients, median age 45 (range 16–67 years); multi-a.; prospective (not associated with HE)	Acute exacerbation of CHB (27)
Garg et al. [14], India	91 patients, median age 36 (range 15–80); multi-a.; prospective (grade I–II and III–IV)	Chronic liver disease: HBV (34), alcohol (31), cryptogenic (22), Wilson's disease (3), autoimmune hepatitis (1); acute insult: reactivation of HBV (29), acute alcoholic hepatitis (25), unknown (15), HEV (14), DILI (3), cytomegalovirus (2), HBV (1), HAV (1), exacerbation of autoimmune hepatitis (1)
Huang et al. [16], China	190 patients, mean age 45.7 (range NR); multi-a.; retrospective (grade I–II and III–IV)	HBV (190)
Zheng et al. [17], China	452 patients (242 cohort 1 + 210 cohort 2), mean age, 45.6 (range NR); multi-a.; retrospective (grade I–II and III–IV)	HBV (452)
Katoonizadeh et al. [18], Belgium	54 patients, median age 51 (IQR 41–61); multi-a.; prospective (not associate with HE)	Cirrhosis + alcohol (54)
Krishna et al. [19], India	121 patients, mean age 36.3 (range NR); multi-a.; retrospective (grade III–IV only)	Underlying cirrhosis due to: HBV (37), alcohol (13), WD (7), autoimmune (6), HCV (5), alcohol + HBV (3), Budd-Chiari (2), hemochromatosis (2), alcohol + HCV (1), HBV + WD (1), cryptogenic (44) acute liver failure due to: HEV ($n = 80$), HAV ($n = 33$), HEV + HAV ($n = 8$)
Sun et al. [20], China	204 patients (34F), mean age 46.8 (range NR); multi-a.; retrospective (grade III–IV only)	HBV (204)
Cordoba et al. [2], Europe	301 patients, mean age 59 (range NR); multi-a.; prospective (grade I–II and III–IV)	Underlying cirrhosis due to: alcohol 50 %, hepatitis C 20 %, hepatitis C plus alcohol 11.4 %

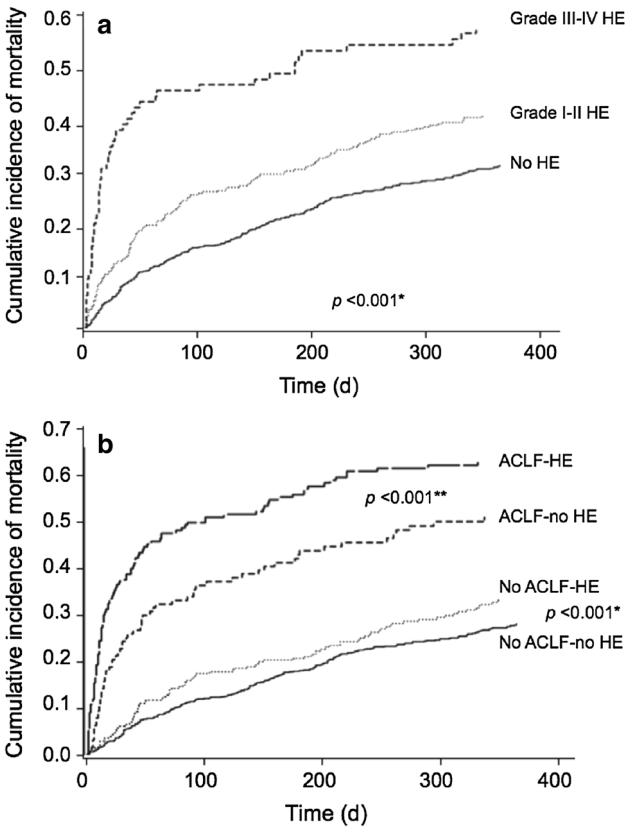

Fig. 1 Mortality of patients included in the study in relation to **a** the severity of HE at inclusion; **b** the presence of HE or ACLF. (Reprinted from [2])

III, SOFA) have shown better reliability than the Child-Pugh or the Model for End-Stage Liver Disease (MELD) to identify patients with bad prognoses [13].

Eight studies [2, 14–20] investigated hepatic encephalopathy as a prognostic factor for acute-on-chronic liver failure. Six studies found a positive association between HE and mortality in a univariate test, and five of them maintained this relationship in the multivariate analysis. Two studies did not find an association with mortality in a univariate test (see Table 1).

The Canonic Study is a prospective observational multicenter international investigation promoted by the EASL-Chronic Liver Failure Consortium. Twenty-nine Liver Units from eight European countries participated in the study. The study described the diagnostic criteria, prevalence, characteristics, grades of severity, natural course, predictors of survival and potential mechanism of ACLF [21]. With this definition, it becomes obvious that HE can appear as an isolated syndrome or as part of ACLF, probably having different characteristics and outcomes.

The mortality probability was significantly higher in patients with HE compared to those without HE (Fig. 1a); it increased significantly as the HE grade worsened. The mortality probability of patients with ACLF was much higher than that of patients without ACLF, independently of the presence or absence of HE (Fig. 1b). In each subgroup (with and without ACLF). the mortality probability was significantly higher in patients with HE [2].

The independent risk factors of mortality at 28, 90 days and 1 year in patients with HE at enrollment were older age, higher levels of bilirubin, INR, sodium and creatinine (Table 2).

Compared with the US Acute Liver Failure (ALF) data ($n = 1{,}696$) [22], the mortality of ACLF patients with grade I–II and grade III–IV hepatic encephalopathy appears to be better than in those with high-risk etiologies (hepatitis B, autoimmune, drug-induced and indeterminate), but poorer than in those with lower risk etiologies (acetaminophen overdose, hepatitis A, ischemic hepatitis and acute fatty liver of pregnancy) of acute liver failure (Fig. 2). Direct comparison is not possible because of the more hetergenous, dual-etiology nature of ACLF and the high risks of late mortality (>200 days) compared with the relatively early mortality in ALF.

Correlation of HE grading to the degree of cerebral edema

Cerebral edema is rare even in ACLF patients presenting with high-grade hepatic encephalopathy. In a recent study from King's College Hospital [23], 1008 patients with CLD were admitted. One hundred seventy-three patients

Table 2 Risk factors for short, mid- and long-term mortality in patients with HE. (Reprinted from [2] as in Fig. 1)

	28 days		90 days		365 days	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age, year (continuous)	1.03 (1.01–1.05)	0.002	1.04 (1.02–1.05)	<0.001	1.03 (1.02–1.05)	<0.001
Bilirubin, mg/dl (continuous)	1.05 (1.03–1.07)	<0.001	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.05)	0.001
INR	1.92 (1.50–2.46)	<0.001	1.83 (1.46–2.30)	<0.001	1.91 (1.54–2.37)	<0.001
Creatinine, mg/dl (continuous)	1.35 (1.20–1.52)	<0.001	1.30 (1.16–1.46)	<0.001	1.26 (1.12–1.42)	<0.001
Sodium, mmol/l (continuous)	–		0.96 (0.93–0.99)	0.004	0.96 (0.94–0.99)	0.004
HE grade (III–IV vs. I–II)	2.60 (1.70–3.99)	<0.001	1.99 (1.35–2.95)	<0.001	1.63 (1.14–2.33)	0.008

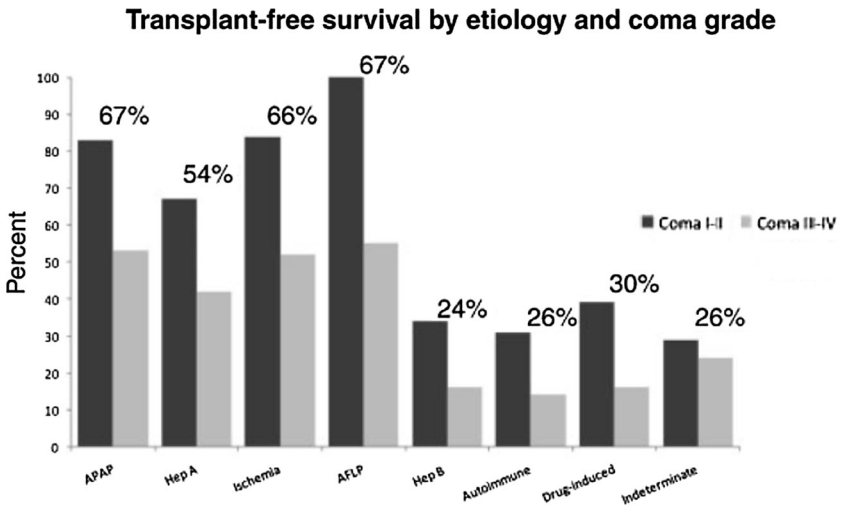

Fig. 2 Acute liver failure survival by etiology and coma grade. (Reprinted from [22])

Table 3 In vivo MRI studies of the brain in acute, acute-on-chronic and chronic liver failure (Chavarria et al. [24]; with kind permission from Springer Science and Business Media)

Studies	Animal model	MRI						Edema	References
		Tl (ms)	T2 (ms)	MTR (%)	ADC/MD	FA	CS	Absolute quantification	
Experimental									
CLF	PCA		≈		≈			≈[a]	Chavarria et al. [40]
	BDL		≈		≈			≈[a,b]	Chavarria et al. [24]
ACLF	BDL + LPS		≈		≈			↑[a]	Chavarria et al. [24]
ALF	PCA + HAL		≈		↓			↑[a]	Barba et al. [41], Chavarria et al. [40], Zwingmann et al. [42]
	HA (NH_4Ac)	↓	↓		↑/↓[c]				Cauli et al. [43]
	GalN				↑/↓[c]			↑[a]	Cauli et al. [52]
Human									
CLF		↓	↑	↓	↑	↓	↑	↑	Rose et al. [53], Cordoba et al. [44], Lodi et al. [45], Kale et al. [46], Shah et al. [47], Nath et al. [25], Chavarria et al. [48]
ACLF					≈	↓	↑		Nath et al. [25]
ALF		↓	≈		↓	↓	↑		Ranjan et al. [49], Rai et al. [50], Saksena et al. [51]

CLF chronic liver failure, *ACLF* acute-on-chronic liver failure, *ALF* acute liver failure

Animal model: *PCA* portocava anastomosis, *BDL* bile duct ligation, *LPS* lipopolysaccharides, *HAL* hepatic artery ligation, *HA* hyperammonemia by ammonia infusion, *Ac* acetate, *GalN* galactosamine injection

MRI: *T1* Tl relaxation time, *T2* T2 relaxation time, *MTR* magnetic transfer ratio, *ADC* apparent diffusion coefficient, *MD* mean diffusivity. *FA* fractional anisotropy, *CS* spherical anisotropy

[a] Quantification by no MR technique

[b] Results with discrepancies depending on the BDL studies

[c] Changes depending of the studied region

(110 male) underwent neuroimaging. Eighty-one (48 male) fulfilled the criteria for ACLF. Variceal bleeding (30 %) and sepsis (31 %) were the most frequent precipitants of ACLF. Of those with neuroimaging from the total cohort, 30 % of CT scans were normal, 30 % demonstrated increased cerebral atrophy for age, 17 % small vessel disease and 16 % intracranial hemorrhage (ICH). Cerebral edema was seen in three patients with ACLF only. An increased prevalence of ICH was observed in the ACLF group (23 vs. 9 %, $p = 0.008$).

MRI brain with diffusion studies is a more sensitive imaging modality to detect cerebral edema than CT (Table 3), so the proportion of patients with ACLF and mild cerebral edema may be higher than reported.

In the only study that correlates hepatic encephalopathy grading with cerebral edema in ACLF [25], 23 patients with ACLF were studied and compared with 15 healthy controls and 15 patients with CLF. Diffusion tensor imaging (DTI) metrics including fractional anisotropy (FA), mean diffusivity (MD), linear anisotropy (LA), planar anisotropy (CP) and spherical isotropy (CS) were calculated by selecting regions of interest in the white matter and deep grey matter of the brain. Significantly decreased FA and increased CS were observed in the anterior limb (ALIC) and posterior limb (PLIC) of the internal capsule and frontal white matter ($p < 0.05$) in patients with different grades (1–4) of ACLF when compared with healthy controls.

However, the clinical utility of these specialized MR techniques in ACLF has not been sufficiently studied.

Treatment strategies

Treatment of ACLF includes treatment of the precipitating event with intensive care and organ support as needed. For hepatic encephalopathy, the established strategies for reducing bacterial translocation have focused on decreasing gut-derived toxins such as ammonia through the use of laxatives such as lactulose.

Improved understanding of the pathophysiological factors involved in the development of ACLF has led to new therapeutic strategies targeting different points on this axis. However, evidence of such treatments were generally derived from small clinical trials or animal models, or based on studies in cirrhotic patients without ACLF; thus, their applicability to ACLF patients should be interpreted with caution.

Antibiotics may decrease gut-derived toxins and endotoxin from entering the portal circulation. There may also be other attendant benefits in terms of reducing immune activation and the inflammatory response with downstream effects on circulatory and end organ dysfunction. Norfloxacin decontaminates the intestine and is well established in the prophylaxis of spontaneous bacterial peritonitis. In addition to targeting translocation from the gut, it may also ameliorate hyperdynamic circulatory changes in cirrhosis [26–28].

Rifaximin treatment is effective for treatment of acute HE and recurrent HE in cirrhotic patients [29, 30]. In one study, rifaximin therapy was associated with no change in ammonia levels but increased levels of the anti-inflammatory cytokine IL10 [31]. Rifaximin has also been shown to improve systemic hemodynamics, portal pressures, endotoxin and proinflammatory cytokine levels and renal function [32, 33]. Furthermore, rifaximin can modulate the metabiome in patients with cirrhosis and HE, causing a shift from pathogenic to beneficial gut bacteria, and reduce endotoxemia [34].

The success of these gut-focused antibiotic therapies strongly support the role of the gut microbiome and translocation in hepatic encephalopathy and ACLF. A number of studies showed that probiotics improved hepatic and systemic hemodynamics in patients with cirrhosis and ascites as well as HE [35–37]. HMG-CoA inhibitors (statins) appear of particular interest as an emerging therapy in that they target various pathophysiological aspects of portal hypertension but may also improve outcomes in sepsis, which is of potential relevance in ACLF [38]. Obeticholic acid, FXR agonist, was demonstrated in a cirrhotic rat model to improve portal pressure by decreasing intrahepatic vascular resistance without causing systemic hypotension [39]. This may potentially reduce portal venous shunting and improve hepatic encephalopathy in cirrhotic patients.

Although the principles of therapy based on the current understanding of the pathophysiology are sound, further studies, specifically in ACLF patients with hepatic encephalopathy, are required to confirm their usefulness, some of which will undoubtedly lead to improving outcomes.

Compliance with ethical requirements and Conflict of interest This article does not contain any studies with human participants or animals performed by any of the authors. Guan-Huei Lee declares that he has no conflict of interest.

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