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].

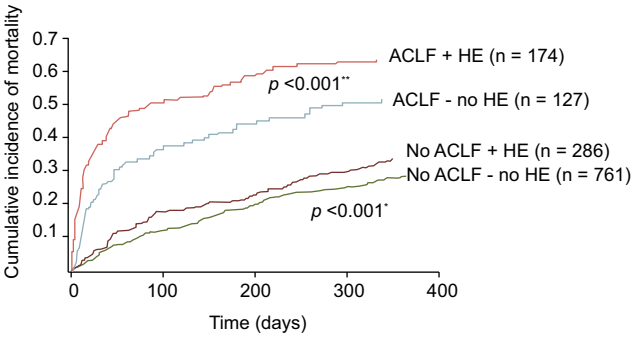

Fig. 1. Actuarial survival curve of hospitalized cirrhotic patients showing mortality of patients with or without ACLF in combination of with or without overt hepatic encephalopathy. Mortality rate was significantly higher in patients with ACLF and HE in comparison with non-HE patients with ACLF. In 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

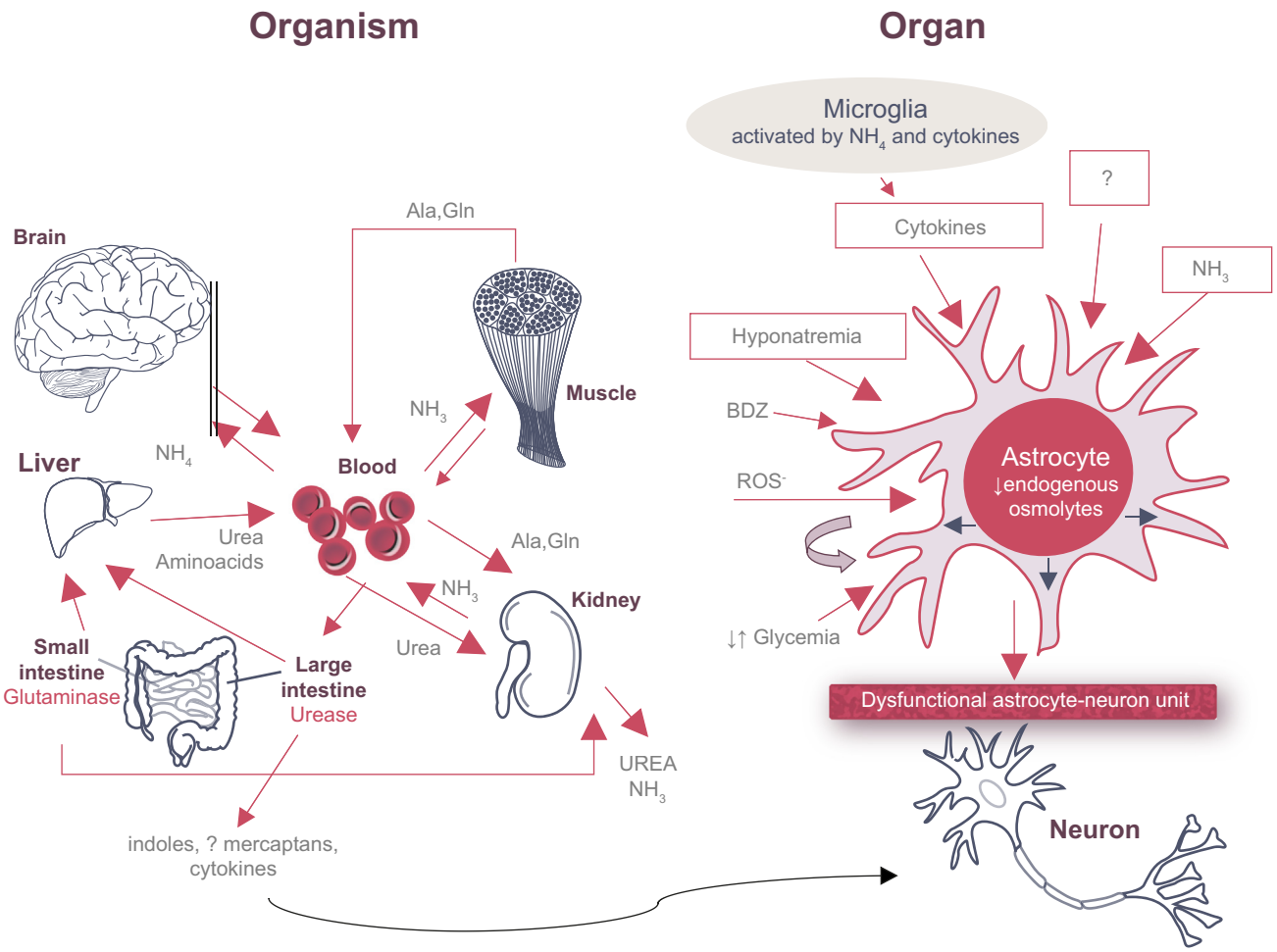

Fig. 2. Ammonia trafficking in hepatic encephalopathy (HE) from an organism (left panel) and an organ (right panel) perspective. A modified nitrogen balance and changes in ammonia production/disposal lead to hyperammonaemia. Hyperammonaemia, together with hyponatremia, increased levels of pro-inflammatory cytokines, an activated microglia and a number of other mechanisms lead to astrocyte swelling. In turn, this results in dysfunctional astrocyte-neuron interactions and, ultimately, in neuronal dysfunction. Other neurotoxins, such as cytokines, indoles and possibly mercaptans may also affect neurons directly. Adapted from Amodio P., Hepatic Encephalopathy in Cirrhosis: a practical guide to management [Moreau & Lee Eds, Oxford University Press (in press)].

be protective in animal models of HE, modulating neuroinflammation [29,30]. However, these therapeutic approaches did not reach applicability in humans. Precipitating factors for HE, such as sepsis, hyponatraemia, gastrointestinal haemorrhage and renal failure are known to share different pathophysiological mechanisms beyond increasing TNFα production or COX-1 activity [31].

Hyponatremia is a major confounding factor in the pathophysiology of HE in patients with ACLF and it could be very difficult to differentiate between hepatic and hyponatremic encephalopathy. Hyperammonemia in ACLF would cause an increased intracellular content of glutamine and osmolality, due to glutamine synthase activity, resulting in astrocyte swelling and astrocyte dysfunction enhanced by oxidative stress. Astrocyte swelling triggers a signalling cascade, increasing formation of reactive nitrogen and oxygen species, mainly through activation of NADPH oxidase and nitric oxide synthase [32]. Reactive nitrogen and oxygen species enhance protein tyrosine nitration, mobilization of zinc, oxidation of RNA, alterations in intra- and intercellular signalling and in gene transcription [33]. Whether the brain is directly involved in the inflammatory process in chronic liver failure or whether it is the systemic response that spills into the brain is not clear [34,35] (Fig. 2). Lastly, hyponatremia could represent a second osmotic hit to astrocytes that could aggravate the intracellular oedema. [36]. Renal ammoniagenesis increases during haemodynamic disturbances in cirrhotics characterized by effective hypovolemia secondary to splanchnic arterial vasodilation, similar to that associated with renal failure, hyponatremia, hypokalaemia, dehydration, or use of nephrotoxic agents, highlighting the key role of the kidneys on hepatic encephalopathy. In a large cohort of 562 cirrhotic patients, the main causes of renal insufficiency were infections, hypovolemic conditions, hepatorenal syndrome and nephrotoxic agents. Hepatic encephalopathy, hyponatremia and MELD predicted prognosis according to the different causes of AKI [37].

Bacterial translocation (BT) and microbiome

Bacterial infections are well-known triggers for HE in patients with cirrhosis [38]. Multifactorial damage of the intestinal barrier results in a high rate of intestinal bacteria translocation in cirrhotics, resulting in systemic inflammation [39,40]. Therefore, BT

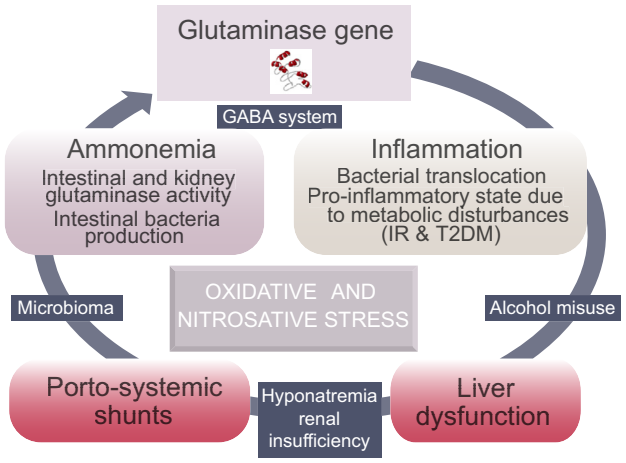

Fig. 3. Pathophysiology of hepatic encephalopathy. Hyperammonemia, systemic inflammation and oxidative and nitrosative stress in patients with liver dysfunction and/or portosystemic shunts modulated by glutaminase gene alterations are key factors and therapeutic targets on hepatic encephalopathy.

may have a role in the pathogenic mechanisms involved in HE, due to circulating endotoxins, which activate macrophages to produce TNFα and other potentially cytotoxic pro-inflammatory mediators [41]. Indeed, a high frequency of small-intestinal bacterial overgrowth (SIBO) in cirrhotic patients has been correlated with BT [42]. On the other hand, microbiota could play a relevant role, irrespective of bacterial translocation. The dysbiosis rate, calculated as the ratio of autochthonous to non-autochthonous taxa, was related to hepatic encephalopathy. Patients developing overt HE during the follow-up demonstrated a lower rate of dysbiosis in comparison with compensated cirrhosis. Besides, the dysbiosis rate was associated with endotoxin levels; the higher the endotoxemia, the lower the dysbiosis rate [43,44].

Diabetes mellitus (DM) and insulin resistance (IR)
Diabetes mellitus (DM) and insulin resistance (IR) was recently shown to be more frequently (59% *vs.* 43%) associated with the presence of HE [45], which was confirmed in another study [46]. The mechanisms underlying this may be related to increased glutaminase activity in the kidney, liver and small intestine [47]; increased pro-inflammatory cytokines such as TNFα and IL-6, resulting in systemic inflammatory response [48]; increased protein catabolism and ammonia production [49] act upon the role of insulin to stimulate protein synthesis as well as on the inhibition of protein degradation; and a reduction in duodenum-cecal transit time due to autonomic neuropathy, resulting in constipation and SIBO [50].

Alcohol misuse
The CANONIC study demonstrated alcohol misuse was strongly related to HE in younger patients with ACLF. The disturbances in hepatic haemodynamics in alcohol-related ACLF have been found to associate with inflammation, multiorgan failure and marked activation of the sympathetic nervous system, supporting a specific role of alcohol in the development of HE, both in alcohol-related decompensation or alcohol-induced ACLF [51].

The GABA system
The potential role of γ-aminobutyric acid-(GABA) or glutamate-mediated neurotransmission in the pathophysiology of HE, together with roles for neurosteroids or endogenous benzodiazepines or other neurotransmitters like serotonin, dopamine, adenosine and histamine have been recently revised [52]. The high complexity of brain circuitries, controlled by multiples types of GABAergic interneurons and the large variety of GABA-A receptors precluded defining a more clear and specific role of GABA on HE [53].

Genetic factors
The human glutaminase gene (OMIM: 138280) is located on chromosome 2 (2q32-q34) [54]. In a prospective study (109 patients with cirrhosis in the estimation cohort, 177 patients in the validation cohort, and 107 healthy controls), Romero-Gómez *et al.* identified a microsatellite in the promoter region of the glutaminase gene (kidney type) containing between 8 and 29 GCA repeats. The longest microsatellite correlated with higher glutaminase activity *in vivo.* It increased the risk for overt HE in cirrhotic patients from 20% to 40% (hazard ratio 3.12 [CI: 1.39–7.02]; $p = 0.006$) [55]. Furthermore, they carried out a functional analysis that showed how longer forms of the microsatellite repeat promoted higher activity *in vitro*, which may increase ammonia production [56]. Therefore, the authors concluded that this genetic difference in the conversion rate of glutamine to ammonia, possibly explained at least in part the variability in the clinical presentation of HE (Fig. 3). Mayer *et al.* confirmed these results in a cohort of 158 patients with liver cirrhosis. The long-long homozygous form (also called major homozygous) was independently associated with HE [57].

Diagnosis and differential diagnosis of hepatic encephalopathy

Definitions and general issues

HE is characterized by a wide spectrum of nonspecific neurological and psychiatric abnormalities [58]. In order for such abnormalities to be qualified as HE one should: (1) confirm that the degree of hepatic failure and/or portal-systemic shunting is severe enough to be able to cause HE, and (2) exclude other causes of neurological and psychiatric dysfunction. Basic as it may seem, this diagnostic procedure is neither routine nor necessarily straightforward. In relation to point 1, measurement of fasting ammonia levels is a reasonable start, because the absence of hyperammonemia makes it extremely unlikely that the observed neuropsychiatric abnormalities are due to HE. Therefore, finding normal ammonia levels in a confused, disorientated or comatose cirrhotic patient should prompt immediate search for alternative causes of neuropsychiatric dysfunction. Point 2 is more complicated, because patients with end-stage liver disease are prone to several types of metabolic encephalopathy (for example uremic and nutritional encephalopathy), and also to non-metabolic neuropsychiatric dysfunction (for example alcohol-related dementia and cerebrovascular disease). These can obviously co-exist with HE, somewhat hampering the 'exclusion diagnosis' procedure [59]. In addition, two common complications of end-stage liver disease, hyponatremia and inflammation/infection, are capable of causing neuropsychiatric dysfunction in the absence of cirrhosis. However, they have also been convincingly shown to act synergistically with gut-derived neurotoxins in determining neuropsychiatric dysfunction in experimental models of HE and in the clinical setting

Table 1. Diagnosis and differential diagnosis of hepatic encephalopathy (HE).

	STEP 1	STEP 2
	Confirm that the degree of hepatic failure and/or portal-systemic shunt is severe enough	Exclude other causes of neurological and/or psychiatric dysfunction
Debated issues		• Border between hepatic and hyponatremic/septic encephalopathies • Neurological and/or psychiatric comorbidity
Practical suggestions	• Standard indices of hepatic failure (Child-Pugh, MELD scores) • Confirmation of the presence/absence of significant portal-systemic shunt	• Neuropsychiatric profiling (please refer to text). Structured questions aimed at assessing orientation to time/space. Glasgow Coma Scale for uncooperative patients • Simple but quantitative nutritional assessment and estimate of recent dietary and fluid intake • History taking, aimed at identifying obvious precipitants and previous episodes of HE, especially if requiring hospitalisation • Full blood count, liver/kidney function, electrolytes, ammonia, TSH, CRP, glycaemia, vitamin B12 and urine analysis • Cerebral imaging should be performed if the clinical profile is unusual, the onset of symptoms is abrupt/severe, if there are focal neurological signs and limited or no response to treatment • Evaluation of the response to treatment (of the precipitant and/or ammonia-lowering strategies)

[19,60,61]. For example, cognitive impairment (overt or subclinical) has been documented in 42% of patients with cirrhosis without infection, in 79% of those with infection and in 90% of those with sepsis [19]. Thus, in patients with cirrhosis, the pathophysiological and clinical borders between hepatic and hyponatremic/septic encephalopathy may be less obvious than in healthy or other disease controls. In addition, in everyday practice it is reasonable and routine to treat them simultaneously. By contrast, one should be absolutely clear that neuropsychiatric abnormalities, related to hypoglycaemia, hypothyroidism, hypoxia, the desired or undesired effects of drugs, such as opioids or benzodiazepines should be qualified as such and not as HE, even when they occur in cirrhotic patients [62]. Differential diagnosis is crucial for two reasons: (i) the encephalopathy we refer to in order to define ALF or ACLF needs to be *hepatic* encephalopathy; (ii) the wrong attribution of neurological/psychiatric symptoms to HE might prevent the diagnosis and the correct management of other causes of neuropsychiatric dysfunction, which are unlikely to benefit from ammonia-lowering drugs or from transplantation. Multiple underlying mechanisms of altered mental status in a patient with cirrhosis should be sought for and treated individually.

In order to tackle these diagnostic issues, it may be useful to draw suggestions from the more general literature. From a psychiatric perspective, episodic overt HE can be classified as a delirium [63], an etiologically nonspecific syndrome, characterized by disturbances in cognition and consciousness, development over a short period time, and fluctuation over time [64]. Delirium is common in hospitalized and critically ill patients. Within this context, its pathophysiology is largely unknown, and generally assumed to be mixed [65]. Interestingly, a recent review on delirium in the ICU does not indicate that efforts are, or should be made to establish the pathophysiology of a delirium episode [65]. It follows that treatment is empirical rather than aetiological [66]. Exactly as it happens with HE, it has also been estimated that non-specifically trained staff can miss the diagnosis of delirium in almost 70% of cases [67]. Efforts have recently been directed towards the prediction of delirium. A large study by van den Boogaard and co-workers defines the likelihood of developing delirium in the ICU based on 10 risk factors that are readily available within 24 h of admission: age, APACHE-II, urgent admission category, infection, coma, sedation, morphine use, urea level and metabolic acidosis [68]. This kind of research seems well directed, because a diagnosis of delirium has been associated with increased mortality [69] and also with impaired long-term cognitive performance [70].

Practical diagnostic recommendations

Despite the highlighted difficulties, some practical recommendations for the diagnosis of overt HE in a hospitalized cirrhotic patient can be formulated (Table 1).

Clinical features and clinical scales

Albeit non-specific, there is a neuropsychological profile to HE type A. Patients with mild overt HE may be inappropriate and euphoric, but higher grades tend to be almost invariably characterized by slowness (in mentation, motion and verbal production), disorientation, the presence of flapping tremor, excessive daytime sleepiness, all the way to lethargy and coma. Focal neurological signs are rare while bilateral Babinski may be observed. Obvious extrapyramidal signs and hepatic myelopathy are also rare but should be considered, especially in male patients with documented large shunts and a history of multiple, severe episodes of HE [71]. While the patient is still awake and cooperative, verbal abilities tend to be preserved, thus obtainment of substantially adequate answers to simple questions ('Good morning, how are you today?') may lead to false reassurance. In contrast, questions should be aimed at specifically assessing orientation to time and space, possibly in a structured fashion [72,73]. Scales, such as CHESS and the Modified-orientation log have been

suggested to be useful in this respect [74]. Recording of the results of such evaluations in the notes may simplify monitoring, also across different nurses/physicians and over subsequent shifts. If the patient is not cooperative, the Glasgow Coma Scale should be utilized both at baseline and over the subsequent monitoring phases [75].

History taking and patient profiling

History taking from cooperative patients or from relatives/caregivers should be aimed at identifying obvious precipitants such as constipation, symptoms of chest, urinary tract or other infections, gastro-intestinal bleeding and dehydration. If identified, these should be corrected. A history of previous episodes of HE, especially if requiring hospitalization, increases the likelihood of the current episode being due to HE and should be recorded. Finally, it should be taken into account that HE associated with ACLF tends to occur in younger cirrhotics with alcohol-related disease and a systemic inflammatory reaction, bacterial infections, active alcohol misuse and/or dilutional hyponatremia [6].

Laboratory tests

A panel of laboratory tests to include full blood count, liver and kidney function, electrolytes, ammonia, TSH, CRP, vitamin B12 and a urine analysis should always be obtained, and abnormalities, such as anaemia, hypo/hyperglycemia or hyponatremia should be corrected. Active alcohol misusers can be considered thiamine/vitamin deficient by default and supplemented.

Ammonia, given its central pathogenic role and known problems with its measurement, deserves further comment. There is probably limited advantage in measuring arterial compared to venous ammonia levels, which can be considered acceptable [76,77]. Venous blood should be preferably drawn when the patients is fasting, in a tube with a stabiliser, refrigerated on ice, sent to the lab immediately and analysed immediately. If arterial or capillary ammonia are utilized, the appropriate reference values should be obtained and utilized. Capillary ammonia is best measured on blood obtained from the earlobe, as sweat artefact leads to significant overestimation on blood drawn from the fingertip [78,79]. Finally, it should be noted that ammonia measurements are problematic in terms of false positives and not false negatives, thus the exclusion of HE based on normal ammonia levels is unlikely to be fraught by measurement issues. Along these same lines, the recently published joint EASL/AASLD guidelines suggest that if ammonia levels are normal the diagnosis of HE is in question. In addition, they warn against the use of high ammonia levels alone for the purpose of diagnosing, staging and formulating prognosis [80].

Imaging

Cerebral imaging should be performed if the clinical profile is unusual, if the onset of the symptoms is abrupt and severe, if there are focal neurological signs and if there is limited or no response to treatment of the precipitant and/or to ammonia-lowering strategies. In most routine, practical conditions, a brain CT without contrast is sufficient, as it allows to diagnose/rule out cerebral and subdural haemorrhage. Structural MRI is probably more appropriate to better define dementia-like, prolonged confusional states and to diagnose/rule out encephalitis and Wernicke's disease.

Neurophysiological tools

The EEG, although non-specific, provides information on the severity of HE in both cooperative and uncooperative patients, it may be useful to monitor them and may help for the inclusion of HE in indices aimed at transplant selection procedures [81]. The grading of the severity of EEG alterations in HE can be based on visual pattern recognition, which has limited reliability and reproducibility, on semi-quantitative evaluation of the frequency, or on automated, spectral analysis of the digitalized tracing. Spectral analysis is more accurate and less operator-dependent. Its value was recently confirmed [82] and a large, validated observational study suggests that the addition of a spectrally derived EEG index improves the predictive value of MELD. The EEG can be recorded at any stage of the patient's evolution, and it can be used to monitor the severity of HE over time and the response to treatment in an objective fashion, regardless of patient cooperation. As sedation, psychoactive drugs and hypothermia can produce EEG alterations not unlike those, which characterize HE, these should be considered as confounders in the diagnostic process. In severe coma, combinations of sensory evoked potential indices can contain information on residual cortical or sub-cortical activity [83]. Neurophysiological monitoring of HE due to acute liver failure would seem reasonable but experience is limited.

Response to treatment

Unless contraindicated, an attempt at non-aggressive bowel cleansing and/or ammonia-lowering treatment can be considered part of the diagnostic armamentarium. A neuropsychiatric syndrome that responds to ammonia-lowering strategies is likely to be HE.

Management of hepatic encephalopathy in a hospitalized cirrhotic patient

Treatment of the acute episode

General measures and monitoring

Early risk stratification of patients with HE is required. This may be performed using the CLIF organ failure scoring system to determine whether the patient has ACLF or not [5]. If a patient has ACLF and associated HE, then he should be managed in an intensive care unit. Detailed description of organ support is outside the scope of this article and has been reviewed elsewhere [84]. The role of monitoring ammonia levels, jugular venous oxygen saturation, evoked potentials, EEG or intracranial pressure remains unascertained.

Airway, breathing, and circulation. Admission to the intensive care unit for close monitoring and airway protection should be considered in all patients with overt HE but particularly if this is associated with ACLF or if the airway is considered to be at risk. Short acting drugs should be used for sedation if needed because benzodiazepines can stay in the circulation for a long time. Hypercapnia and hypoxia should be avoided as they may alter cerebral blood flow. Supplemental oxygen or mechanical

ventilation should be used as required. Inotropes should be used to maintain mean arterial pressure to ensure adequate cerebral perfusion [85].

Role of the precipitating event. Although the prevalence of a precipitating event is more common in patients with ACLF compared to those without, in about 40% patients no precipitating event was found [6]. The most common causes were the use of diuretics suggesting intravascular volume depletion, bacterial infection and alcohol binge. Gastro-intestinal bleeding, as a precipitating event, was under-represented in patients with HE. Any identifiable precipitating event should be promptly treated, cultures performed from multiple sites and, appropriate and early antibiotics should be administered (Fig. 4).

Glucose, nutrition, and electrolytes. Hypoglycemia should be corrected and patients monitored to prevent further hypoglycemic episodes. Hyperglycemia should be prevented as this can make brain swelling worse but there is no evidence for a tight control of glucose [84]. Hyponatremia should be prevented by infusion of crystalloids as this can lead to worsening of HE. Hypernatremia can lead to cellular dysfunction and should be prevented. Vitamins, particularly thiamine should be administered to patients with underlying alcoholic liver disease to prevent occurrence of Wernicke's encephalopathy, particularly when glucose containing fluids are administered. Low protein diets have not been shown to prevent recovery from HE and should be avoided as this can lead to protein breakdown. A restricted protein diet was compared with normal protein diet, which showed that the wake-up rate for the patients in both groups was similar but increased protein breakdown was observed in patients treated with a low protein diet [86]. A detailed guidance on the nutritional management of patients with HE was recently published [87].

Specific

Ammonia Ammonia, a physiologic product of the intermediary metabolism, is composed of nitrogen and hydrogen. The human body has several sources of ammonia: (a) glutamine deamidation by glutaminase (GLS) in the small intestine; (b) urea and nitrogenous compound hydrolysis by gut bacteria [88]; (c) ammonia production and excretion in the kidneys. In the healthy state, hepatic metabolism of ammonia takes place in two areas: (1) in periportal hepatocytes, through the urea cycle (the most important pathway); (2) in pericentral hepatocytes, transforming small quantities of ammonia into glutamine through the action of glutamine synthase [89]. In cirrhosis or in the presence of portosystemic shunts, the liver is by-passed and ammonia detoxification takes place in the muscle through glutamine synthesis by glutamine synthetase [90]. Furthermore, the kidney is an organ capable of synthesizing and degrading ammonia, depending upon the clinical situation [91,92].

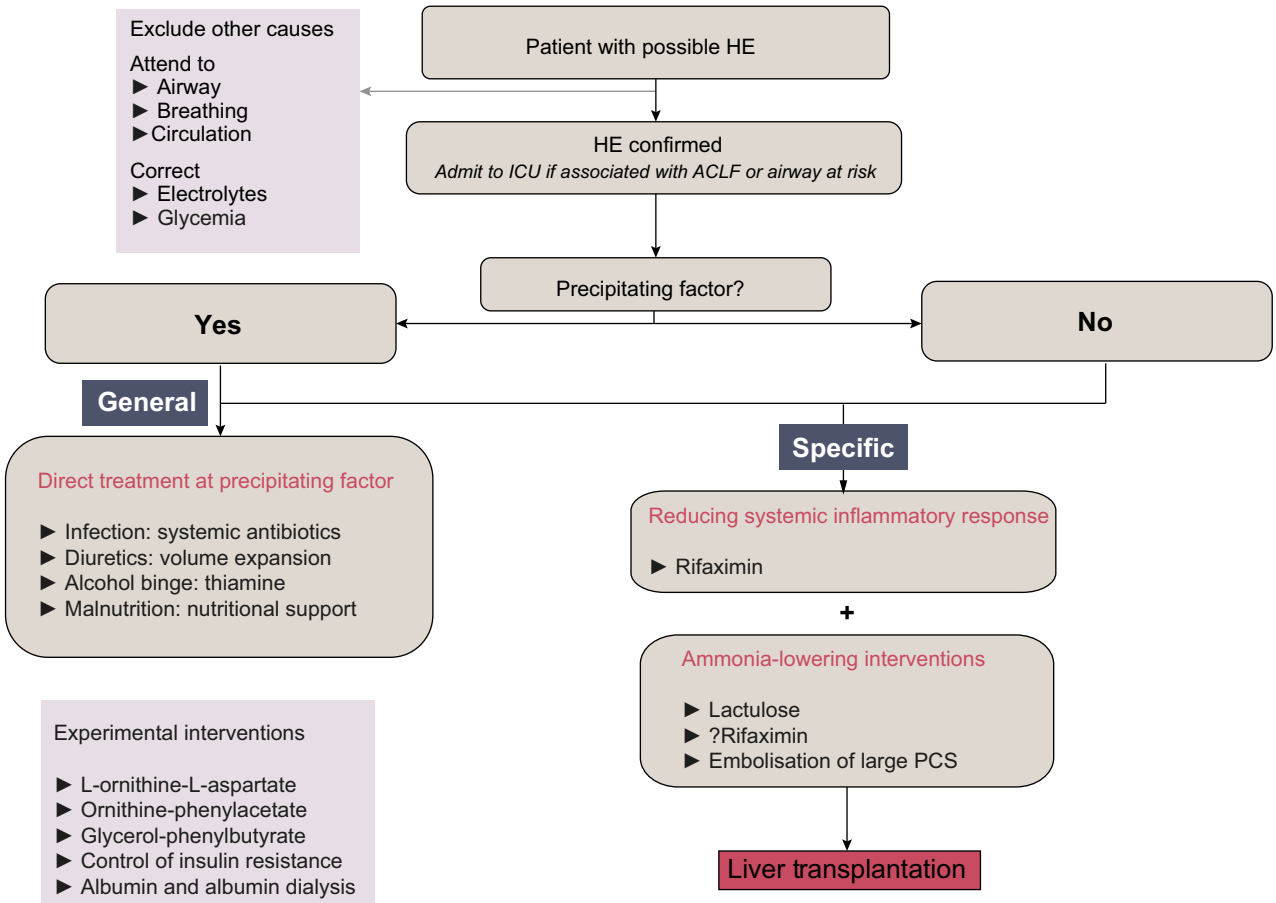

Fig. 4. An algorithm for the management of hepatic encephalopathy in a hospitalized cirrhotic patient.

At present there is no drug that has been consistently shown to reduce ammonia by targeting its metabolism in hospitalized cirrhotic patients. Some new approaches to treat hyperammonemia combine potential ammonia-lowering agents together with products able to promote glutamine excretion. Ornithine phenylacetate (OP) is a drug that stimulates hepatic and muscle glutamine synthesis through the action of ornithine and traps ammonia in form of glutamine, which is then removed following conjugation with phenylacetate [93]. In an open-label study, OP was shown to prevent the rise in ammonia concentration in cirrhotic patients presenting with a gastro-intestinal bleed [94]. A randomized study is underway. Another interesting approach that has not been tested in this population is a drug that has been used to treat urea cycle enzyme disorders, glycerol phenylbutyrate. This compound acts by scavenging glutamine, a precursor of ammonia and was shown to be useful in the secondary prophylaxis of HE in a phase 2b study [95]. Furthermore, L-ornithine-L-aspartate was found superior to placebo improving neuropsychiatric alterations and decreasing ammonia levels in a meta-analysis. The analysis omitted the results of some studies [96].

Targeting the gut. The mainstay of therapy of a hospitalized patient with cirrhosis is lactulose, which acts by reducing the absorption of ammonia by converting it to ammonium in the colon. It has recently been shown to prevent the occurrence of HE in patients with a gastrointestinal bleed [97]. There is a lack of good data comparing lactulose against placebo in patients with advanced HE [98], but this approach remains to be thoroughly tested in clinical trials. The administration of enemas to clear the bowel is a useful adjunct to lactulose but the frequency of administration; type of enema to be used and clinical efficacy need to be better defined. A major advance in the management of HE was the introduction of rifaximin, a non-absorbable antibiotic. While its use has been confirmed in the secondary prophylaxis of HE [99], its role in the management of the hospitalized cirrhotic remains to be validated. A special population of patients are those undergoing insertion of a transjugular intrahepatic portosystemic stent-shunt. A randomized study comparing lactulose, rifaximin and placebo were unable to confirm the benefit of any these approaches to prevent the occurrence of HE [100].

Albumin and albumin dialysis. Albumin is more than just a volume expander and may have important detoxification properties, modulating inflammatory response and endothelial function [101]. In an early controlled study, the potential role of albumin in HE was observed in patients with diuretic-related HE [102]. This approach was tested in a randomized controlled clinical trial [103], which found that although there was no significant difference in the resolution of HE between the groups, survival was enhanced in the albumin group, suggesting that the trial was underpowered. The potential beneficial effects of albumin were translated into studies where the patient's plasma was dialysed against albumin using the molecular adsorbent recirculating System (MARS). In an early randomized study, a beneficial effect on HE was observed without any significant effects on ammonia [104]. These observations were confirmed in a large randomized, multicentre clinical trial, showing incontrovertibly that those patients, not responding to the best standard of care, had significant improvement in HE and time to reduction in severity, when treated with MARS [105]. These observations were confirmed in a multicentre randomized clinical trial in patients with ACLF, the RELIEF trial [106]. Although overall survival was not improved, a significant effect on HE was observed in a subgroup analysis.

The role of benzodiazepine antagonists. Flumazenil, a benzodiazepine receptor antagonist has been trialled in patients with HE based upon the concept that endogenous benzodiazepines may contribute to hepatic encephalopathy. The data suggest that this approach is safe and may be particularly relevant in patients with HE related to iatrogenic administration of benzodiazepines. A further limitation is the short half-life of the drug [107].

Embolization of portacaval shunts. One of the main contributors to the development of HE is portacaval shunting. Large spontaneous portacaval shunts, usually present with persistent HE, can result in hospital admission with advanced coma. In some patients with HE, large spontaneous shunts that are accessible to embolization, may benefit. In a retrospective cohort study this approach was shown to be of benefit in about 70% of patients, particularly if their MELD score was 11 or less [108]. These data were confirmed in another retrospective controlled clinical study [109]. Randomized controlled data are not available and it is clear that many patients will not benefit and also have portal hypertension related complications. Therefore, patient selection is extremely important.

TIPSS-related hepatic encephalopathy. De novo HE can affect up to 30–50% of patients who undergo TIPSS [110] and this can sometimes be severe enough to result in cerebral oedema and coma [111]. The mechanism of this is complex and related to a combination of hyperammonemia, increased portosystemic shunting with resultant endotoxemia, and alterations in cerebral blood flow [112]. Treatment options are limited and a randomized trial of lactulose or rifaximin, used prophylactically, was not shown to be useful [100]. Patients with troublesome HE after TIPSS respond well to shunt occlusion, which remains the therapy of choice [113].

Role of liver transplantation

A hospitalized, critically ill cirrhotic patient with HE should be worked up from a transplant perspective. Transplantation itself and subsequent immunosuppressant treatment are risk factors for both neurological and psychiatric dysfunction, in the immediate and long-term post-transplant period, respectively [64]. Patients that are transplanted with severe multiorgan failure, including severe HE, can have a good outcome with liver transplantation. Over 85% mortality was observed in patients with 3 or more organ failures without liver transplantation. This was reduced to a mortality of 20% with early liver transplantation [5]. However, at present there is no priority for severe HE patients on the waiting list for transplantation where organ allocation is based on the MELD score, which underestimates the risk of death [80]. A new scoring system has been developed and validated by the CLIF consortium, which needs further evaluation before it can be implemented for the clinical allocation of organs [114].

Conclusions

In conclusion, HE in a hospitalized patient, particularly when it is associated with ACLF, is associated with a high mortality rate independent of other organ failures. The mechanism of HE in

ACLF is not clear but cerebral oedema affects a relatively small group of patients and although ammonia is important, the systemic inflammatory response plays an important part. Glutaminase gene alterations seem to modulate the HE risk and may allow selection of patients for prophylaxis. Treatment options are limited. It is clear that HE in ACLF patients is distinct clinically, prognostically and pathophysiologically to the conventional forms represented in type A, B and C. If the current observations are borne out by other ongoing studies, then it should perhaps be classified into a separate group, type D.

Conflict of interest

M. Romero-Gómez is the inventor of THDP-17, a glutaminase inhibitor, which was licensed by Janus Developments. He has ongoing research collaboration with Umecrine, Sweden. He has also received speaker fees from BAMA-GEVE, Merz, and Norgine. R. Jalan is the inventor of ornithine phenylacetate, which has been licensed to Ocera Therapeutics. He has ongoing research collaboration with Gambro and Grifols. He has also received speaker fees from Grifols and Norgine. S. Montagnese has received speaker fees from Merz and her institution has received funding from Merz to support research conducted by her team.

Authors' contributions

M. Romero-Gómez, S. Montagnese, and R. Jalan shared writing of the manuscript.

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