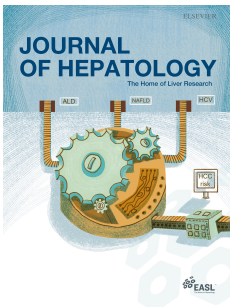

Heretical thoughts into Hepatic Encephalopathy

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Heretical thoughts into Hepatic Encephalopathy

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Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Discovery, a spin out company from University College London, Hepyx Limited and Cyberliver. He has research collaborations with Takeda and Yaqrit Discovery.

Christopher Rose has research collaborations with, and is an advisor for Aza Technologies, Axcella, Horizon Therapeutics, Lupin Pharma, Mallinckrodt, Morphocell Technologies and Neuractas.

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Key Words

Hepatic Encephalopathy

Ammonia

Lactulose

Rifaximin

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Abbreviations

Hepatic Encephalopathy: HE

Minimal Hepatic Encephalopathy: mHE

Acute Liver Failure: ALF

Acute on Chronic Liver Failure: ACLF

Portosystemic Shunting: PSS

Hepatic Encephalopathy Staging Tool: HEST

Food and Drug Administration (FDA)

Hepatorenal Syndrome (HRS)

Author's Contributions

Both Prof Jalan and Prof Rose have contributed equally to scientific rationale, generation of the idea, data collection, data analysis, writing and critical review of the manuscript.

Data availability

No original data are described in this paper. The source of all the data used in this paper are referenced.

Summary

Clinical progress in the development of new diagnostic modalities and therapeutic strategies for the management of patients with hepatic encephalopathy has lagged behind the vast knowledge that has been generated from basic studies. In this article, we critically assess matters that should be revisited such as definition, classification, diagnosis and grading of hepatic encephalopathy that are difficult to apply reproducibly using the current criteria. Many lines of investigation have confirmed that hepatic encephalopathy is irreversible in many patients and suggests the need for further studies focussing on mechanisms of neuronal injury and death to guide future drug development for these patients. The clinical evidence behind using lactulose for all severities of hepatic encephalopathy, which is currently considered the standard of care is poor and placebo-controlled trials for hepatic encephalopathy should be considered ethically sound. This expert opinion identifies current challenges in hepatic encephalopathy and highlights areas which require further debate and investigation in order to help advance the field both scientifically and clinically.

Hepatic encephalopathy (HE) research, development of diagnostic tests and treatments remain rudimentary despite many advances in understanding the basic biology of this condition. Unfortunately, there are many remaining issues that need to be addressed to impact clinical management and outcomes of this debilitating syndrome. In this article, we highlight matters that we believe need attention so that reduction in the morbidity and mortality of patients with HE can be achieved. We attempt to identify areas and concerns which we believe require further investigation. We have chosen the title carefully to reflect the objective of this paper which includes the deliberate attempt to be provocative. The manuscript will focus on definition, classification, diagnosis, irreversibility, and treatment.

Definition

Currently, the term 'hepatic encephalopathy' is defined as 'brain dysfunction caused by liver insufficiency and/or portosystemic shunting (PSS)' [1]. There are many problems with this definition. *First*, it is incorrect to refer to patients with PSS and no liver disease (currently classified as Type B HE) with brain dysfunction as having 'HE' since the liver is normal. Clearly, the prognosis, pathophysiology, and management options for PSS are distinct from patients with advanced liver disease. Moreover, infants born with urea cycle disorders that develop hyperammonaemia-induced neurological dysfunction are not diagnosed as having HE since liver disease is not present [2]. Hyperammonemia leads to brain dysfunction, a commonality in all 3-conditions; liver disease, PSS and UCD. However, since PSS and UCD do not have underlying liver disease, brain dysfunction in these patients should not be described as HE. Instead this term should be reserved for patients with liver-disease, hyperammonemia induced brain dysfunction. *Second*, 'liver insufficiency' is a broad

term that is poorly quantified and can range from trivial abnormalities of liver function (based on plasma liver enzyme levels, transient elastography; non-functional analysis) to fulminant liver failure. *Third*, the causes of liver injury such as alcohol abuse, obesity and metabolic associated fatty liver disease, Hepatitis C and co-morbidities such as hypertension and diabetes may impact brain function independent of the severity of liver disease [3]. Since these disorders can induce neurological dysfunction, independent of the impact of severity of liver disease, it is critical to define HE with a liver-disease specific neurotoxin. The best validated biomarker in this context is hyperammonaemia. *Fourth*, brain dysfunction arising during acute liver failure (ALF) (currently classified as Type A HE) is characterised by brain edema and risk of intracranial hypertension, due to very different pathophysiological mechanisms and different clinical challenges than those with HE on the background of cirrhosis [3]. This entity, although under the umbrella of HE, should be considered separately. Furthermore, it is important to classify brain dysfunction in patients with acute-on-chronic liver failure (ACLF), which is clinically, pathophysiologically and prognostically distinct from patients with decompensated cirrhosis and no ACLF [4]. *Fifth*, a small proportion of patients with cirrhosis develop overt motor disturbances (Parkinsonian features) while others develop paraplegia (hepatic myelopathy) [5,6]. These are extremely rare syndromes that are poorly characterised both clinically and pathophysiologically. Some early studies indicate that hepatic myelopathy is caused by demyelination of corticospinal tract in the spinal cord with no clinical or pathophysiological link to HE [7]. Parkinsonian syndrome, likewise, is very poorly understood and response to conventional therapies of HE does not improve outcomes and rather dopaminergic treatments are tried [5]. There are only isolated case reports showing their improvement with liver transplantation [8]. Lumping them together with

conventional HE is inappropriate, and we feel they should be classified as 'variant forms' of neurological dysfunction in patients with liver disease.

The complexity of brain dysfunction in patients with liver disease is highlighted in Figure 1a. To navigate through some of the intricacies in relation to classifying HE, we believe minimum diagnostic criteria need to be developed to help define the syndrome. The term 'HE' should be reserved for dysfunction of the brain that is a consequence of cirrhosis or ALF and associated with hyperammonemia. (Figure 1a).

Staging and Classification

HE is currently staged according to the modified form of the West Haven criteria [1]. Table 1a summarises this grading system and questions their relevance, emphasizing the likelihood of a large variability in the way these criteria are clinically assessed. Hepatic Encephalopathy Staging Tool (HEST) was developed for assessing the severity of HE as an end point and approved by the US Food and Drug Administration (FDA). It appears to be more objective and easier to apply [9] (Table 1b). HEST (Table 1b) allows distinction between grade 1 from 0 HE. However, it does not consider mHE. Patients (without asterixis) who respond correctly to all 5 questions gets defined as grade 0. Patients (without asterixis) who incorrectly answer one of the 5 questions, get defined as grade 1. Patients (with asterixis) who incorrectly answer one of the 5 questions, get defined as grade 2. However, this promising tool requires further validation.

As stated in the current guidelines, HE should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors

(Figure 1b) [1]. However, classifying patients with ALF as having either covert or overt, episodic, recurrent or persistent and, spontaneous or precipitated is not clinically relevant.

Furthermore, complexity and confusion have been created by the introduction of the term ’covert’, which encompasses all patients with mHE and Grade 1 HE under a single category (Figure 1b). The term ‘covert’ attempts to simplify the classification but in our view, this nomenclature is confusing and should be re-visited. Literally, ‘covert’ means ‘hidden’. However, patients with Grade 1 HE are symptomatic and clinical signs can be elicited [10]. Moreover, the risk of complications of cirrhosis, mortality and severity of systemic inflammation are significantly higher in patients with Grade 1 HE compared with those with mHE [10]. Therefore, to combine these very disparate entities (non-symptomatic (mHE) with symptomatic (Grade 1)) under a single domain appears to be an oversimplification. The diagnosis of mHE is even more challenging. There are several psychological/psychometric tests presently available, which questionably evaluate different elements of brain function. Their widespread usability, clinical utility, specificity, prognostic and pathophysiological correlates remain unclear and require large multicentre studies to provide further clarity. Furthermore, the impact of previous episodes of overt HE on ongoing abnormalities in these tests remains unknown and should be further evaluated.

Diagnosis of HE and the role of ammonia measurement

For decades, hyperammonemia leading to neurotoxicity has been shown to be the cardinal pathogenic factor in the pathogenesis of HE in patients, animal models and cell systems [11]. Undeniably, the diagnosis of HE is based on clinical judgment and

subsequently the pathogenic factor should be identified and corrected. Remarkably, in 30% of cases of HE, precipitating and pathogenic factors are not identified. Many lines of investigation show that a diagnosis of HE is incompatible with normal ammonia levels although a direct relationship between grade of hyperammonemia and severity of HE is lacking. However, elevated blood ammonia can predict HE-related hospitalizations and established cut-offs of blood ammonia have been demonstrated in many different studies to have prognostic value [12–14]. Furthermore, a change in the severity of hyperammonenia in patients with HE, defines the risk of death arguing for the value in serial measures of ammonia (Table 2). It is, therefore, inevitable to state that without an increase in blood ammonia, a diagnosis of HE is not tenable. However, despite the overwhelming evidence for the role of ammonia measurement in the diagnosis and prognosis of HE, it is not routinely measured, nor is its measurements recommended in the current guidelines. Rather, pragmatic treatment with lactulose and/or rifaximin is started. An inadequate clinical response to medical therapy signifies exclusion of the diagnosis of HE and differential diagnosis is considered. There are many hindrances with this approach. First, treating HE without identifying the pathogenic factor reduces the potential effectiveness of current interventions [15]. Second, response to therapy should not be used as a diagnostic tool to define HE, particularly since neither lactulose has not been shown in placebo controlled clinical trials to be useful in overt HE. Third, the time required to wait for a response to treatment can be vital as duration of HE episode (>48hrs) can have a significant impact on mortality [16].

The recently published Rahimi study (Phase 2b efficacy of ornithine phenylacetate) was the first trial designed to randomize patients with HE and hyperammonemia and

to demonstrate ammonia as a valuable companion biomarker in HE [9]. In this study, 231 patients with cirrhosis with overt HE (> grade 2) were randomised to receive ornithine phenylacetate or placebo [9]. The protocol stipulated that randomisation was to take place if blood ammonia levels were elevated (>upper limit of normal). The primary endpoint was not reached as the drug did not lead to a significant reduction in time to improvement of overt HE. However, when the ammonia levels were measured in a central laboratory, the investigators showed that in 30 patients, ammonia levels were normal at the time of randomisation. Upon a post-hoc analysis including the 201 patients with elevated ammonia levels, statistically significant results in time to clinical improvement in overt HE was observed in the group treated with the active agent. These data argue strongly for the use of ammonia as companion biomarker to guide HE therapy with a drug known to target ammonia. This is particularly relevant for development of new treatments for HE.

As illustrated in Table 2, the existing data show very clearly that a diagnosis of HE cannot be sustained if ammonia levels are normal and reveal the important diagnostic and prognostic role of ammonia. We believe minimum criteria are required to diagnose HE. Some of the elements that may be pertinent and applicable are the following.

- Presence of cirrhosis or ALF
- Pathophysiological basis (hyperammonemia)
- Brain imaging to exclude other causes
- Some measure of neurological dysfunction such as abnormal EEG, which has shown specificity for HE or alternative psychological/psychometric tests used to detect mHE. [17]

This suggested approach will need to be validated in future studies.

Lessons from other complications of cirrhosis

Other main complications of liver disease have reliable clinical features or biomarkers.

- Portal hypertension: hepatic venous pressure gradient; transient elastography combined with platelet count, presence of varices; splenomegaly
- Renal dysfunction: creatinine
- Ascites: ultrasound, clinical examination
- Infection: cultures for bacteria, inflammatory markers
    - spontaneous bacterial peritonitis: neutrophil count in ascitic fluid

Similarly, elevated glucose has high predictive value for the risk of diabetes and its complications [18]. The current predicament with ammonia and HE parallels what was previously the case with hepatorenal syndrome (HRS). Historically, all patients with cirrhosis who presented with acute kidney injury were indiscriminately diagnosed with HRS. Today, HRS has specific diagnostic criteria with potential introduction of new biomarkers [19]. Although there is some degree of overlap with non-HRS acute kidney injury, HRS is a relatively specific entity.

It is however important to indicate that the measurement of ammonia is only clinically useful if measured meticulously using standardized protocols. We hope this article encourages clinicians to engage with their clinical and biochemical teams to develop appropriate standard operating procedures. Indeed, the false positives (30/231; 13%) observed in the Rahimi et al. study provides evidence that ammonia measurements can only be interpreted if performed properly. Implementation of methods to correctly

analyse ammonia may well be challenging but worthy in management and providing appropriate therapy for patients.

Irreversibility

Since HE is defined as a neurological disorder due to liver disease, in theory it should be reversible with liver transplantation. However, many reports have shown that patients having received a liver transplant, who had a history of HE, do not normalize their neurologic state [20] suggesting that HE is not always reversible. However, it remains unknown what pathophysiological factors and conditions (preoperative, operative, postoperative) precipitate neuronal cell death and contribute to this irreversibility [21]. Interestingly, it is recognized that the duration of hyperammonemia and/or the concentration of blood ammonia can influence neuronal cell survival [22]. The latter is difficult to explore in patients without serial (or home monitoring) ammonia measures. Based on these observations, one could argue that HE should be treated as a medical emergency in the same way as myocardial infarction and cerebrovascular accident are currently managed. Greater emphasis should be placed on attempts to prevent the first episode of HE.

For decades, astrocyte swelling has been thought to be the central neurological marker in the pathology of HE [23]. However, the precise role of astrocyte swelling in the pathogenesis of HE remains undefined. Undoubtedly, a physiological or metabolically impaired swollen astrocyte will lead to weakened astrocyte-neuronal communication and compromise brain function[24]. However, the manifestations of HE is the result of multiple pathogenic factors which trigger changes in cerebral bioenergetics, mitochondrial dysfunction, oxidative stress and neuroinflammation.

Future studies should explore interventions that target these newly discovered important pathophysiological pathways and better define the mechanisms underlying irreversibility.

Treatment

The current 'standard of care' therapy for HE, independent of severity, is lactulose, a disaccharide proposed to have different mechanisms of action including reducing ammonia absorption, acting as a pre-biotic and altering the microbiome [25]. However, lactulose is a laxative and whether other laxatives are equally beneficial remains unknown. Although there are many controlled clinical trials which have investigated the effect of lactulose on the severity of HE, a great proportion of these studies are open to bias since most are neither double blinded nor placebo controlled and are single-centre studies. As illustrated in Table 3, 11 placebo-controlled clinical trials with lactulose have been conducted, each with an average of 22 patients (number of patients in individual studies ranging between 6-40). A total of 246 patients were studied between 1969 and 1997 with very different designs, type of placebo used, dose of lactulose administered, inclusion and exclusion criteria and, clinical outcomes. More importantly, the placebo used in all these studies were inappropriate as none of them produced a laxative effect allowing inevitable unblinding. Moreover, there is lack of clarity on whether the trials were independently monitored (for the variables such as inclusion and exclusion criteria; end points) and compliance is not clearly documented. It is clear from existing clinical experience that lactulose is a difficult treatment to tolerate and is associated with many unfavourable side effects. Although serious adverse events are rare, flatulence, diarrhoea, dehydration are frequent, which occasionally result in hyponatremia and acute kidney injury [26].

Taken together, lactulose as a treatment for HE does not endure the rigour that is required for approval of new treatments. Even though lactulose can be useful in patients with cirrhosis patients who are admitted stuporous, particularly if they are constipated, lactulose is not an FDA-approved indication for either the treatment or the prevention of HE. Therefore, we believe that lactulose should not considered standard of care until more robust data from adequately powered, independently performed, monitored, placebo-controlled, randomised, double blind and multicentre studies are available. The choice of such a placebo for comparison with lactulose is complex but would require a laxative component to avoid unblinding. We, therefore, propose that placebo-controlled trials of lactulose are needed to confirm that this drug indeed should be considered standard of care. Also, placebo-controlled trials of potential new treatments should be considered ethically sound given the paucity of high-quality data showing superiority of lactulose compared with placebo. To achieve these aims, the regulators, governing boards of responsible societies and patient groups will need to be convinced.

Conclusions

With the advances in the knowledge and understanding of what constitutes evidence, we believe a relook at the many aspects of HE is essential if we want to have a positive impact on this terrible complication of cirrhosis. There are important lessons to be learnt from how the other liver-related complications such as renal dysfunction and HRS have been re-classified. Introducing clarity to the nomenclature, classification, diagnostic criteria, pathophysiology, and standard of care are crucial in designing

clinical trials, identifying sound clinical end points with the ultimate aim of improving patient care.

Legends to Figures

Figure 1a: Hepatic encephalopathy and brain dysfunction in patients with liver disease. Brain dysfunction can occur under multiple conditions with or without liver disease. Therefore, hepatic encephalopathy should not be defined by specific symptom(s) but rather by the presence of cirrhosis or acute liver failure and, the presence of hyperammonemia, the causal agent. Many co-factors as illustrated can act synergistically with hyperammonemia to produce hepatic encephalopathy but by themselves do not cause hepatic encephalopathy in the absence of hyperammonemia.

Figure 1b: Classification of hepatic encephalopathy according to the type of underlying disease, severity of manifestations, time course, and precipitating factors. *(modified from Vilstrup et al. J Hep 2014)*

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Table 1a. Modified West-Haven criteria as described in the current guidelines and the problems with their assessment

Grade	Clinical criteria	Relevance to diagnosis and grading
Unimpaired	No HE	'Normal' needs to be defined. No pertinent tests have been identified.
	No history of HE	No data on whether all patients with previous HE will continue to have brain abnormalities
Minimal	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	The currently used tests to diagnose mHE such as the PHES test, CFF lack specificity. EEG is likely to be more specific but not as sensitive.
1	Trivial lack of awareness, euphoria or anxiety	The terms such as 'trivial' 'euphoria' 'anxiety' 'shortened attention span' 'impairment' are extremely nonspecific and subjective, therefore, are not useful in clinical practice, research and drug development.
	Shortened attention span	Tests need to be specified
	Impairment of addition or subtraction	Need to clarify degree of complexity
	Altered sleep rhythm	Altered sleep rhythm is likely due to altered 'clock' and is non-specific.
2	Lethargy or apathy; obvious personality change, inappropriate behaviour; dyspraxia	The terms 'lethargy', 'apathy' 'personality change', 'inappropriate behaviour' and 'dyspraxia' are nonspecific and not quantitative.
	Disorientation for time and asterixis	Disorientation and asterixis are more specific but not sensitive.
3	Somnolence to semistupor; responsive to stimuli; bizarre behaviour	The terms 'somnolence', 'responsive to stimuli' and 'bizarre behaviour' are non-specific and difficult to quantify.
	Confused; gross disorientation	'Confused' and 'Gross disorientation' are clearer yet their severity is not quantifiable
4	Coma	Although this is clear, its degrees are not quantifiable.

Table 1b. Hepatic encephalopathy staging tool

Stage	Criteria
0/1	No asterixis[a] and no disorientation based on the following 5 questions (ie, patient provides a correct response to questions 1, 2, 3, 4 and 5): 1. What is your name? 2. What city are we in? 3. What type of place is this? (correct answer: hospital) 4. What is the year? 5. What is the month?
2	Asterixis and disorientation based on the following 5 questions (ie, any single incorrect response qualifies the patient as stage 2 for questions 1, 2, 3, 4, or 5): 1. What is your name? 2. What city are we in? 3. What type of place is this? (correct answer: hospital) 4. What is the year? 5. What is the month?
3	Stupor, arousable out but falls asleep, responsive to verbal stimuli Obvious confusion Gross disorientation
4	Coma

NOTE. Patients (without asterixis) who respond correctly to all 5 questions gets defined as grade 0. Patients (without asterixis) who incorrectly answer one of the 5 questions, get defined as grade 1. To qualify for study entry as stage 2 hepatic encephalopathy, both asterixis and ≥ 1 error in the 5 sentinel questions must have been present at screening and baseline. For recording hepatic encephalopathy response after starting study drug infusion, patients were classified as improved to stages 0/1 only if asterixis resolved and all 5 questions answered correctly.
[a]Three or more flaps/30s indicates asterixis. Modified from Rahimi et al. CGH 2020

Table 2. Evidence for the importance of ammonia measurements in the diagnosis and prognosis of patients with hepatic encephalopathy

Study	Aim	Study Design	Number of patients included	Main Results	Conclusion
Clemmensen et al. 1999	To examine the hypotheses that high arterial ammonia is related to death by cerebral herniation	Prospective and retrospective single centre study	22 patients with ALF and 31 with HE (22 with ALF and 9 with ACLF)	Ammonia levels were higher in patients with ALF who developed cerebral herniation. They identified a cut-off of 150umol/L.	In ALF, high ammonia level is associated with cerebral herniation
Jalan et al. 2004	To determine the role of inflammation in the pathogenesis of intracranial hypertension in patients with ALF and its interplay with cerebral blood flow and ammonia	Prospective single centre study. Measurements were made prior to any specific treatment for intracranial hypertension	21 patients with ALF and grade IV HE divided in two groups: 1) ICP>20 mmHg and 2) ICP≤20 mmHg	Inflammatory markers, ammonia and CBF were higher in those with ICP>20	Ammonia and inflammation play synergistic role in intracranial hypertension in ALF patients
Kundra et al. 2005	To compare plasma ammonia levels in patients with ALF or CLD with or without HE; to correlate ammonia levels with the severity of HE and with clinical features of intracranial hypertension	Prospective single centre study. Clinical criteria were used for diagnosis and staging of HE	20 with ALF and 20 with CLD (8 with HE and 12 without HE)	There was good correlation between severity of HE and ammonia. In ALF, ammonia levels of patients with intracranial hypertension/cerebral herniation were significantly higher than those without	There is good correlation between severity of HE and clinical features of intracranial hypertension or cerebral herniation and ammonia levels in ALF
Bhatia et al. 2006	To evaluate the relationship of arterial ammonia levels at admission to complications and survival	Prospective single centre study	80 patients with ALF	Non-survivors had higher median ammonia than survivors. Hyperammonemia was associated with deeper encephalopathy, cerebral oedema, need for ventilation and seizures. A reduction in ammonia level was associated with better outcomes.	Arterial ammonia at presentation is predictive of outcome and can be used for risk stratification. Serial measurement of ammonia provides important prognostic information
Bernal et al. 2007	To evaluate the relation between the arterial ammonia concentrations on admission and survival, risk of subsequent HE and intracranial hypertension	Prospective single centre study	165 patients with ALF and advanced HE, 50 with ALF in the absence of severe HE, 33 with decompensated CLD, and 9 admitted following hepatobiliary surgery	Ammonia was an independent risk factor for the development of severe HE and intracranial hypertension. After admission, ammonia levels remained high in those who developed intracranial hypertension and fell in those who did not.	Ammonia is an independent risk factor for the development of both HE and intracranial hypertension
Niranjan-Azadi et al. 2016	To evaluate the relationship between ammonia levels and mortality in ALF and to	Retrospective single centre study. Patients who required	36 consecutive patients admitted to intensive	Admission ammonia level (>120 µmol/L) was associated with higher mortality rate.	Admission ammonia level is predictive of mortality in

	characterize the subgroup of patients who develop acute kidney injury and require replacement therapy	haemodialysis were compared to those without acute kidney injury	care units with grade III and IV HE		ALF patients with grade 3–4 HE
Ong et al. 2003	To evaluate the relationship between ammonia levels and the severity of HE using venous, arterial and partial pressures.	Prospective single centre study	121 patients with cirrhosis	Each of the four measures of ammonia increased with the severity of HE.	Ammonia levels correlate with the severity of hepatic encephalopathy. Venous ammonia levels are adequate.
Nicolao et al. 2003	To compare venous, arterial and partial pressure of ammonia in cirrhotics with and without HE and controls	Prospective single centre study. Clinical and psychometric evaluation were used to assess HE	27 patients with cirrhosis and HE, 15 cirrhosis patients without HE and 9 controls	HE was associated with higher levels of each form of ammonia. The correlation with the severity of HE was similar for venous, arterial ammonia and partial pressure	Venous ammonia levels allow diagnosis of HE. Arterial levels do not add substantially.
Patwardhan et al. 2016	To determine whether ammonia is associated with transplant-free survival in patients with AD and ACLF	Retrospective single centre cohort study	494 consecutive hospitalized patients (265 with HE)	Every doubling of ammonia was associated with 30- and 90-day transplant or mortality. Patients with ammonia levels >60µmol/L had higher 30- and 90-day risk of death or transplantation	An elevated ammonia on admission is independently associated with reduced 90-day transplant-free survival
Sawhney et al. 2016	To determine the role of ammonia, inflammation, and cerebral oxygenation in ACLF patients with and without HE	Prospective study. Arterial ammonia, JVO2 and white blood cell count were measured consecutively	101 with ACLF admitted to the intensive care unit	Hyperammonemia was associated with the presence and severity of HE; improvement in these parameters was associated with a reduction in HE severity whilst an increase in ammonia increased risk of death	Ammonia, is an important prognostic biomarker and change in its levels are prognostically important
Vierling et al. 2016	To determine the role of blood ammonia levels on mortality and risk of overt HE	Retrospective analysis from prospective multicenter study	178 patients with cirrhosis and a history of 2 episodes of overt HE within the past 6 months	Fasting ammonia levels of >1.5ULN lead to an increased risk of developing an HE event and death within 16 weeks	Fasting ammonia is useful in predicting HE-related morbidity
Ravi et al. 2017	To study the impact of ammonia levels in alcoholic hepatitis	Retrospective single centre cohort study	105 patients admitted with alcoholic hepatitis (51 with HE)	Higher ammonia levels predicted risk of mortality. The addition of ammonia to the regression models improved their performance irrespective of the presence of HE	Ammonia levels predict risk of mortality
Shalimar et al. 2019	To determine the relationship between ammonia and severity of HE and its association with	Prospective observational multicentre study	498 cirrhosis patients admitted with AD	Ammonia correlated with severity of HE and was an independent predictor of 28-day mortality. Lack of improvement in baseline	Ammonia, is an important prognostic biomarker and change in its levels are prognostically important

	organ dysfunction and short-term mortality			ammonia at day 5 was associated with high mortality (70.6%)	
Shalimar et al. 2020	To assess the effect of persistent or incident hyperammonemia on organ failure and outcomes in ACLF	Paired ammonia on day 1 and 3 of admission. Persistent or incident hyperammonemia was defined as ≥79.5 μmol/L on day 3	229 consecutive admissions with ACLF and 83 with no ACLF	Persistent or incident hyperammonemia was associated with new-onset organ failure involving liver, kidney, brain, coagulation, circulation, and respiratory and had higher 28-day mortality	Hyperammonemia independent of ACLF is associated with increased risk of organ failure and death
Hu et al. 2020	To determine the association between ammonia level and short-term prognosis in ACLF	ACLF according to the APASL definition (subanalyses in HBV reactivation)	174 with ACLF (106 with HBV reactivation)	Ammonia was higher in non-survivors and was related to ACLF grade and organ failure. Ammonia was a prognostic factor in HBV reactivation induced ACLF	Ammonia is correlated with organ failure and is an independent risk factor for mortality in ACLF and HBV reactivation related ACLF
Verma et al. 2021	To evaluate the dynamics of HE and ammonia estimation in ACLF	ACLF patients recruited using APASL criteria	3009 ACLF, 1315 (43.7%) with HE at presentation	Ammonia was a predictor of HE occurrence, higher HE grades and 30-day mortality. The dynamic increase in ammonia over 7 days could predict non survivors and progression of HE	Ammonia is associated with the presence, severity and progression of HE and mortality in ACLF
Chiriac et al. 2021	To assess the role of venous ammonia in predicting the outcome of cirrhotic patients with ACLF	Retrospective observational study in ACLF patients using APASL criteria	446 with ACLF	Receiver operating characteristic analysis showed good accuracy for the prediction of short term mortality for ammonia.	Ammonia can be used as a biomarker to predict mortality in patients with ACLF

Studies in ALF patients presented in blue; in cirrhosis and ACLF in black. The table describes a selection of studies.

Abbreviations: acute-on-chronic liver failure (ACLF), acute liver failure (ALF), chronic liver disease (CLD), hepatic encephalopathy (HE), APASL: Asia Pacific Association for the Study of Liver, HBV: Hepatitis B.

References: Clemmesen JO et al. Hepatology, 1999 Mar;29(3):648-53; Bernal W et al. Hepatology, 2007 Dec;46(6):1844-52; Jalan R et al. J Hepatol, 2004 Oct;41(4):613-20; Bhatia V et al. Gut. 2006 Jan;55(1):98-104; Niranjan-Azadi AM et al. Ann Transplant, 2016 Aug 2;21:479-83; Ong JP et al. Am J Med, 2003 Feb 15;114(3):188-93; Nicolao F et al. J Hepatol, 2003 Apr;38(4):441-6; Kundra A et al. Clin Biochem, 2005 Aug;38(8):696-9; Patwardhan VR et al. J Clin Gastroenterol, 2016 Apr;50(4):345-50; Sawhney R et al. Liver Transpl, 2016 Jun;22(6):732-42; Ravi S et al. Gastroenterol Rep (Oxf), 2017 Aug;5(3):232-236; Shalimar et al. Hepatology, 2019 Sep;70(3):982-994; Shalimar et al. JGH Open, 2020 Feb 28;4(5):843-850; Hu C et al. Sci Rep, 2020 Oct 12;10(1):16970; Verma N et al. Hepatol Int, 2021 Aug;15(4):970-982; Chiriac S et al. World J Clin Cases, 2021 Jan 26;9(3):552-564.

Table 3. Characteristics of Clinical Trials of Lactulose vs Placebo

Trial and Year	Trial Design	Number of patients	Definition of HE	Assessment of HE	Active agent (s)	Placebo	Blinding	End Points	Result
Elkington et al. 1969	Double-blind, cross-over, single-centre, inpatient trial	7	Persistent (25%) or previous overt HE (75%)	Mental status (modified Parsons-Smith criteria), arterial ammonia, EEG	Lactulose, Galactose, and Lactose	Sorbitol	Participants and personnel	Efficacy	5 out of 7 patients improved. Stool pH and arterial ammonia were reduced by lactulose; improvement in the EEG occurred in 4 patients
Simmons et al. 1970	Double-blind, parallel-arm, single-centre, inpatient trial	26	Episodic (81%), recurrent (19%)	Mental status, venous ammonia	Lactulose	Glucose	Participants and personnel	Mortality, HE, adverse events	No significant differences
Brown et al. 1971	Double-blind, cross-over, single-centre inpatient/outpatient	20	Persistent	Mental status, blood ammonia, EEG	Lactulose	Sorbitol	Participants and personnel	Long-term efficacy	11 patients responded favourably (2 of them had few months of follow-up), 6 were not taking the lactulose, 3 died early
Germain et al. 1973	Double-blind, parallel-arm, single-centre, outpatient trial	18	Persistent	Mental status (Parson-Smith criteria), psychometric tests, venous ammonia, EEG	Lactulose	Saccharose-based	Participants and personnel	Mortality, HE, and adverse events	No significant differences
Rodgers et al. 1973	Double-blind, cross-over, single-centre, outpatient trial	6	Persistent	Mental status, blood ammonia, EEG	Lactulose	Sorbitol	Participants and personnel	Long-term efficacy	Not significant differences
Corazza et al. 1982	Double-blind, parallel-arm, single-centre inpatient trial	32	Persistent	Mental status, blood ammonia, EEG	Lactulose	Not available	Participants and personnel	Efficacy	Lactulose was better than placebo in lowering ammonia levels.

									Improvement of HE not available
McClain et al. 1984	Double-blind, parallel-arm, single-centre, outpatient trial	32	Not clinical evidence of HE	Psychometric tests	Lactulose	Sucrose	Participants and personnel	Psychometric test	Improvement in three of the five tests in the lactulose group (no improvement in any test in the sucrose group)
Uribe et al. 1987	Double-blind, cross-over, single-centre, outpatient trial	18	Episodic, Persistent	Conn score, Number Connection Test, blood ammonia, EEG	*Lactitol*	Lactose	Participants and personnel	Safety and efficacy	No significant differences
Horsman et al. 1997	Double-blind, parallel-arm, single-centre, outpatient trial	14	Subclinical encephalopathy	Mental status, psychometric tests, venous ammonia, EEG	Lactulose	Lactose	Participants and personnel	Effect of lactulose on psychometric test	Improvement in number connection test (5 out of 7 vs 1 out of 7) and race-track test (24.5% vs 9.8%)
Quero et al. 1997	Double-blind, parallel-arm, single-centre, outpatient trial	40	Minimal HE diagnosed with at least 2 psychometric tests	Mental status, psychometric tests, arterial ammonia, EEG	Lactulose	Lactose	Participants and personnel	Mortality, HE, adverse events, and quality of life	No significant differences
Shi et al. 1997	Double-blind, parallel-arm, single-centre, outpatient trial	31	Minimal HE	Psychometric test, blood ammonia	Lactulose	Glucose	Participants and personnel	Effect of lactulose on psychometric test	Not available

Abbreviations: HE: Hepatic encephalopathy; EEG: Electroencephalogram

References: Elkington SG et al. N Engl J Med, 1969 Aug 21;281(8):408-12; Simmons F et al. Gastroenterology, 1970 Dec;59(6):827-32; Brown H et al. Arch Surg, 1971 Jan;102(1):25-7; Germain L et al. Arch Fr Mal App Dig, 1973 Jun;62(4):293-302; Rodgers JB et al. Am J Gastroenterol, 1973 Nov;60(5):459-65; Corazza GR et al. Int J Clin Pharmacol Res, 1982;2(Suppl 1):7-13; McClain CJ et al. J Clin Gastroenterol, 1984 Aug;6(4):325-9; Uribe M et al. Dig Dis Sci, 1987 Dec;32(12):1345-53; Horsmans Y et al. Aliment Pharmacol Ther. 1997 Feb;11(1):165-70; Quero JC et al. In: Record C, Al-Mardini H editor(s). Advances in Hepatic Encephalopathy & Metabolism in Liver Disease: Proceedings of the 9th International Symposium on Ammonia. Vol. 64, Newcastle upon Tyne, UK: Ipswich Book Company Ltd, 1997:459-65; Shi H et al. Chin J Dig 1997;17:221-3.

Fig 1a

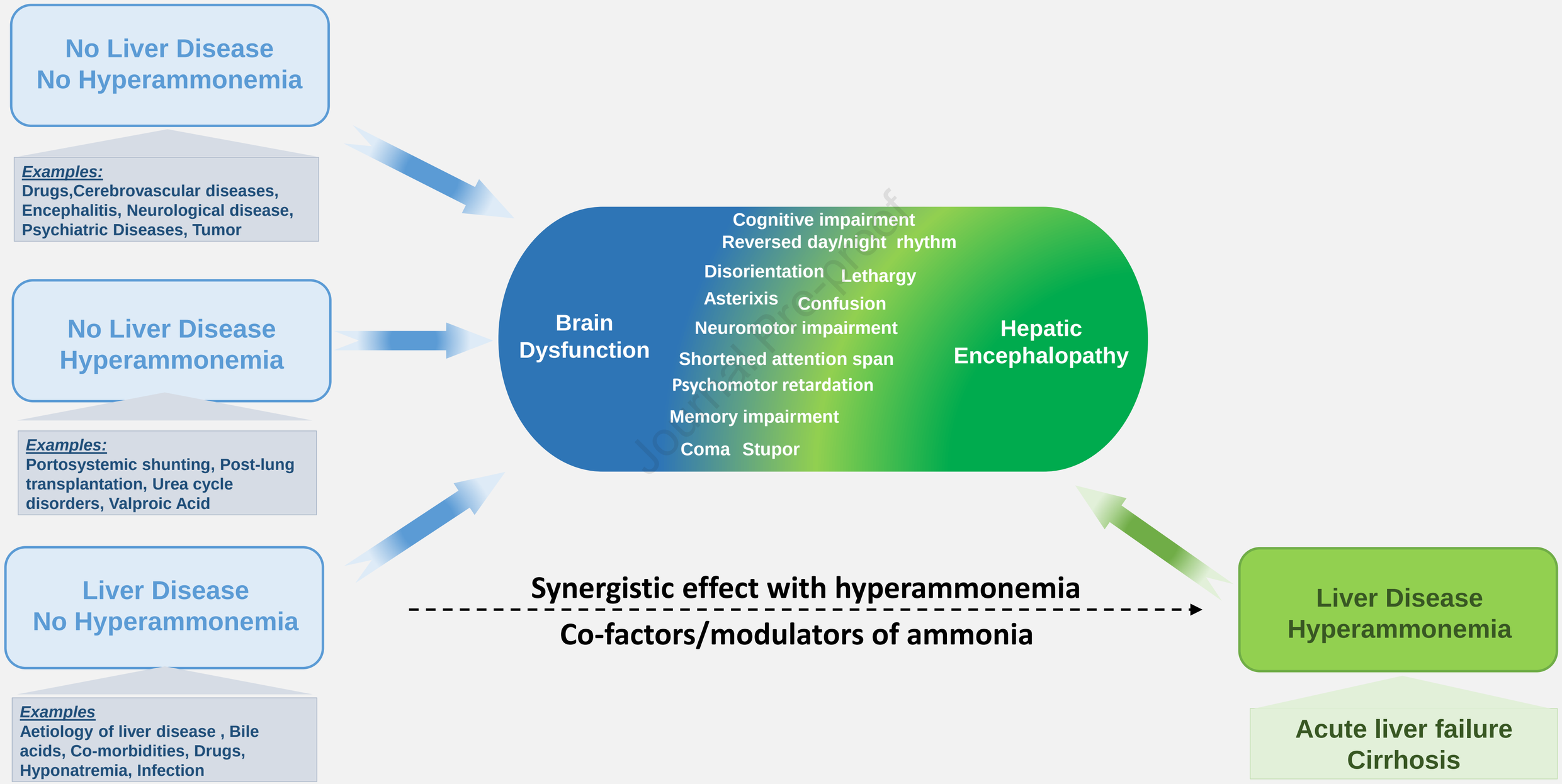

Fig 1b

<table>
<tr><th>Type</th><th colspan="2">Grade</th><th>Time course</th><th>Spontaneous or precipitated</th></tr>
<tr><td rowspan="2">A</td><td>MHE</td><td rowspan="2">Covert</td><td rowspan="2">Episodic</td><td rowspan="2">Spontaneous</td></tr>
<tr><td>1</td></tr>
<tr><td rowspan="2">B</td><td>2</td><td rowspan="3">Overt</td><td rowspan="2">Recurrent</td><td rowspan="3">Precipitated (Specify)</td></tr>
<tr><td>3</td></tr>
<tr><td>C</td><td>4</td><td>Persistent</td></tr>
</table>