Current Diagnosis and Classification of Hepatic Encephalopathy

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Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portal-systemic shunt; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma. It should be differentiated from other neurological/psychiatric disorders that can occur in patients with liver disease. Its classification needs to take into account the underlying condition, severity, course, precipitating factors, and—possibly—sensitivity to ammonia-lowering agents. (J CLIN EXP HEPATOL 2018;8:432–437)

The term ‘hepatic encephalopathy’ (HE) was used by Porter and Adams¹ to refer to the condition that was previously called hepatic coma² and was accurately described and named portal-systemic encephalopathy (PSE) by Sherlock et al.³ The term PSE underlined the link between brain dysfunction (i.e., encephalopathy) and portal-systemic (PS) shunt occurring in cirrhosis, which causes a relevant increase in gut-derived ammonia and, possibly, other gut-derived toxins. In fact, ammonia is a substance with extensive first-pass effect, and thus, its plasma level is massively increased by PS blood shunting. The use of the term HE is preferable to the one of PSE because it underlines that at the basis of the condition, there is a lack of some functions of the liver, independent of this occurring because of PS blood shunting or because of pure liver failure, as it happens in acute hepatic failure.

The observation that liver disease is associated to behavioral changes goes back to Hippocrates, but the first accurate description of the association of cirrhosis with delirium and coma was given by Morgagni in the 18th century.⁴ However, the fundamental pathophysiological insight into the condition was provided by Hann et al.⁵ who were able to induce brain dysfunction in dogs with the creation of PS shunt. They were also able to prove a link with nitrogen metabolism. The power of ammonia to induce coma or stupor in patients with cirrhosis was clearly established in humans in the 30s of the last century by van Coult et al.,⁶ who administered oral ammonia salt loads, and by the comatogenous side effect of the first diuretic substances that increased the ammonia level.⁷ Of

note, the variability of the effect of the same amount of ammonia salt load in the same subjects⁸ clearly proved that the toxic effect of ammonia on the brain is not direct, but mediated by some metabolic processes within the brain and by the interaction with other factors.

THE DIAGNOSIS OF HE

The clear link with nitrogen metabolism and deficiency in ammonia detoxification, which depends on liver function and PS shunt, differentiates HE from other unspecific kinds of delirium (also called ‘encephalopathy’) which easily occur in many severe medical conditions, such as pneumonia, urinary infections, myocardial infarction, hip fractures, hyponatremia, drug toxicity, etc. and is easily seen in elderly people.⁹ Of note, since the half of last century, Riddell¹⁰ stated that: ‘... among a group of patients with severe liver disease a number of neurological disturbances will be met with; not all of these are the disease known as hepatic coma. Among these other states are the psychoses associated with chronic alcoholism and nicotinic acid deficiency, electrolyte disturbances, septicaemia, increased response to narcotics and subdural haematoma’.

Thus, despite its unspecific clinical expression, HE cannot be classified as mere delirium (or ‘encephalopathy’) occurring in patients with liver disease because of its peculiar causal link with liver insufficiency/PS shunt and with the consequently altered metabolism of gut-derived nitrogenous substances.

This is the reason why the American Association for the Study of Liver Diseases/European Association for the Study of the Liver (AASLD/EASL) guidelines stated that ‘HE is a brain dysfunction caused by liver insufficiency and/or PS shunt; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma’.¹¹

A Bayesian approach to the diagnosis of HE is based on the recognition of *i*) compatible clinical findings (Table 1), *ii*) high pretest probability (severe liver failure/PS shunt), *iii*) consideration of obvious alternative causes that can completely or partially explain the findings, and *iv*) at least

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Abbreviations: ACLF: acute-on-chronic liver failure; EEG: electroencephalogram; HE: Hepatic Encephalopathy; PSE: portal-systemic encephalopathy <https://doi.org/10.1016/j.jceh.2018.07.001>

Table 1 Clinical Patterns of HE Presentation—Modified From the Study by Amodio.⁴³

Pattern		Description
A) Coma		The patient's eyes are closed, unresponsive even to pain stimulation
B) Rapidly developing confusion state	Inhibited Agitated	The patient is disoriented in time and/or space and/or identity and somnolent The patient is disoriented in time and/or space and/or identity and agitated/angry/restless
C) Almost continuous mild mental dysfunction with interspersed recurrent episodes of more severe confusion than usual		Dementia-like pattern
D) Predominant motor disorder with mild/moderate mental dysfunction/confusion	Extrapyramidal Pyramidal	Parkinsonism or chorea or athetosis Spastic paraparesis with hyperreflexia
E) Mild brain dysfunction		The patient is oriented, and his/her mental activity seems normal or near-normal; sometimes, caregivers or relatives refer a decay from the patient's standard in terms of behavior, irritability, or cognition. On psychometrical testing, alterations are detectable (they concern attention, working memory, visuo-practical ability, and inhibition). Other signs associated or independent of psychometrical alterations are the slowing of EEG activity and/or the reduction of critical flicker frequency.

Note: In patterns B-D, usually asterixis is present.
EEG, electroencephalogram; HE, hepatic encephalopathy.

some degree of reversibility with treatments improving the derangement of nitrogen metabolism (Figure 1).

Concerning the alternative causes, it should be noted that in single patients, HE can be superimposed to other medical or neurological disorders damaging the brain function because HE—a disorder depending on liver insufficiency/PS shunt—can be overlapped to other conditions damaging the brain function. In this case, proper diagnosis

of each condition is mandatory to allow combined treatments.

Of note, patients with low plasma ammonia levels lack the prerequisite for HE to occur; i.e., severe liver dysfunction and/or PS shunt both of which are reflected by high plasma ammonia levels.^{12–15} Patients with low plasma ammonia may suffer from delirium of any other origin (as any other patients without liver failure), so that accurate investigation of alternative causes is required. In contrast, patients with high ammonia may have *i)* normal brain function, *ii)* HE, *iii)* other brain disorders, and *iv)* overlapped brain disorders. Thus, high ammonia, although a risk factor for the development of HE,¹⁶ is not sufficient for the diagnosis of HE, just as hypercholesterolemia is not a criterion to diagnose myocardial infarction.

Proper diagnosis is relevant for patient management because it is potentially dangerous to miss out the diagnosis of other potentially threatening conditions and treat them with drugs targeted to reduce gut dysbiosis/lower plasma ammonia, such as lactulose, oral antibiotics, L-ornithine-L-aspartate, sodium and glycerol phenylbutyrate, or ornithine-phenylacetate.

THE CLASSIFICATION OF HE

The classification of HE is multi-axial because various dimensions are required for proper management of patients.

Figure 1 Flow chart for the diagnosis of HE—modified from the study by Amodio⁴³—ALAs, ammonia-lowering agents; *high plasma ammonia level is a marker for liver insufficiency and/or portal-systemic blood shunting.

Table 2 Pros and Cons of the Introduction of the Label 'Type D' for HE in ACLF.

Pros	Cons
<p>The higher the characterization of the underlying condition, the higher the likelihood of proper etiologic treatment.</p> <p>HE in ACLF is highly influenced by cytokine storm and MOF, and ICI was reported (despite very rarely).</p> <p>Brain hyperhydration is correlated with HE severity.</p>	<p>Ockham's razor principle: '<i>entities must not be multiplied beyond necessity</i>'.</p> <p>No consensus/proof that further subdivision of HE improves the patient's management more than taking into account analytically all the mechanisms/treatments of delirium/coma in a subject with ACLF and MOF.</p> <p>Mixed metabolic encephalopathy is likely the actual condition.</p>

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy.

HE should be qualified on the basis of 1) the underlying context, 2) the actual severity, 3) the time course, 4) the precipitating factors, if any, and—possibly—5) the response and dependence to hypoammonemic treatments.

Consensus exists that the kind of disorder causing HE should be mentioned because this has pathophysiological, clinical, prognostic, and treatment implication.^{11,17} The main distinction is between HE in the context of acute liver failure (ALF) vs. the one in the context of cirrhosis. More recently, it was found useful to distinguish between HE in cirrhosis vs. the one in patients with noncirrhotic PS blood shunting.^{11,17}

Clearly, HE in ALF (type 'A' HE) has distinct pathophysiological features because it occurs in a context without shunt, with massive systemic inflammation involving the brain, severe systemic and intracranial hemodynamic alterations, and intracranial hypertension that can lead to death because of brain herniation.^{18,19} Thus, it requires specific treatments that differ from those used in patients with chronic disease. In contrast, the distinction between HE in cirrhotic (type 'C' HE) and in noncirrhotic PS shunt (type 'B' HE) is less relevant because the pathophysiology, clinical picture, and treatments are similar. However, this distinction may be useful because *i*) the obliteration of shunt, if possible, resolves the problem in patients with noncirrhotic PS shunt and *ii*) the prognostic implications are clearly different because patients with noncirrhotic portal hypertension and shunt have better prognosis than cirrhotic patients.

Recently, the opportunity to create a further distinction within the patients with cirrhosis between those with and those without acute-on-chronic liver failure (ACLF) was proposed.²⁰ The main reason behind this proposal is the more severe prognostic value of HE in the context of ACLF,²¹ even if there is no proof of peculiar pathophysiological mechanisms.²² The finding that the increased brain water content is parallel with the degree of HE²³ is in line with the view of increased astrocyte hydration in HE.²⁴ It should be emphasized that the concept of brain hyperhydration ('edema') should not be confused with the one of intracranial hypertension. At any rate, in very severe cases of patients with HE and multiorgan failure in the intensive care unit, evidence of intracranial hypertension has been

reported,²⁵ despite autopsy-based evidence of death for cerebral herniation is scanty, if any.

In the context of ACLF, the role of inflammation is greater in patients with ACLF than in patients without ACLF, as well as the role of other noxae in the brain deriving from multiorgan failure, such as hypoxia,²⁶ renal failure, etc. Thus, the risk for mixed metabolic encephalopathy is reasonably higher in this context, so that probably both *i*) personalized treatments might be preferable and *ii*) specific trials might be implemented. Obviously, this might be difficult because ACLF is a syndrome (an umbrella term) combining different pathophysiological conditions. On the other hand, proliferation of headings in any classification should be avoided if their utility is unproven (Ockham's razor principle: "*entities must not be multiplied beyond necessity*") (Table 2).

Thus, consensus about the utility to label HE in ACLF as a type (type 'D') separate from type 'C' will probably depend on the proof that it may require specific diagnostic and treatment procedure that differs from the ones used in patients without ACLF.

The severity of symptoms of HE has an implication on patient care and possibly implies different therapeutic responses^{27,28} and prognosis.²¹ This has been classified in various ways in the past (Table 2); other original and reasonable scoring systems are the Chess scale,²⁹ the Log scale,³⁰ and, more recently, a Delphi-based scoring system.³¹ A not-recommendable tool is the hepatic encephalopathy scoring algorithm (HESA)³² because *i*) no operative definition of the terms is provided, *ii*) the number of items defining a grade is not defined, and *iii*) the progression of items to define a grade is arbitrary (e.g., why tremor cannot appear after slurred speech, or hyperactive reflexes after bizarre behavior?).

A simple way is the one suggested by the AASLD/EASL practice guidelines that introduce operative criteria to improve the classic 4-degree system proposed by Conn and accept the dichotomy between asymptomatic or barely discernible HE ('covert') and highly symptomatic HE ('overt') proposed by an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus.¹¹ Each of the two conditions is heterogeneous and needs further staging. For overt HE, the classical

Table 3 Grading of the Severity of HE (Modified From the AASLD/EASL Guidelines).

ISHEN	WH modified with the insertion of MHE	Description	Operative criteria
Unimpaired		No encephalopathy at all, no history of HE	
Covert	Minimal	Neuropsychological alterations on tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Neuropsychological alterations on tests exploring psychomotor speed/executive functions or neurophysiological/psychophysiological (CFF) alterations without clinical evidence of mental change
	Grade I	<ul style="list-style-type: none"> • Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction 	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his/her standard on clinical examination or to the caregivers
Overt (i.e., undoubtedly symptomatic)	Grade II	<ul style="list-style-type: none"> • Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior 	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, year) ± the other mentioned symptoms
	Grade III	<ul style="list-style-type: none"> • Somnolence to semi-stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior 	Disoriented also for space (at least three of the followings are wrongly reported: country, state—or region, city, place, floor) ± the other mentioned symptoms
	Grade IV	Coma	Do not respond even to pain stimuli

HE, hepatic encephalopathy.

Table 4 Grid Summarizing the Classification Criteria for HE.

Type	Severity	Time course	Precipitation factors	Ammonia-lowering agents
Type A: due to ALF	quantification/neuromonitoring is closely linked to the expertise of ICUs caring for the patients			
Type B: due to porto-systemic shunt, without significant liver disease (e.g. pre-hepatic portal hypertension)	COVERT minimal HE grade 1 West Haven	episodic recurrent (≥2 bouts OHE in 6 months)	No/Yes (possibly report the precipitant factor)	No/Yes (for all conditions)
Type C: liver cirrhosis (both liver failure and porto-systemic shunt)	OVERT grade 2 West Haven grade 3 West Haven grade 4 West Haven (coma)	persistent (dementia or dementia-like)		
Type D* (?): severe ACLF in ICU	Only concerning grades 3-4			

Note: *The utility to consider this subtype is under debate. Possibly it concerns patients with severe ACLF and severe metabolic encephalopathy—possibly of mixed etiology—in the context of MOF.

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy.

criteria implemented by the operative definitions proposed by the AASLD/EASL practice guidelines (Table 3) are easily usable, while the Animal Naming Test³³ is a reasonably short and practical tool to detect and quantify the heterogeneity of the 'covert' condition. A recommendable tool to detect and quantify minimal hepatic encephalopathy (MHE) and, possibly, grade 1 HE is the portal hepatic encephalopathy score (PHES).^{34,35} More sensitive tools, such as computerized tests, might be inadequate to test grade 1 HE because patients may be unable to be tested. In contrast, a relatively easy and low-sensitive technique, such as critical flicker frequency (CFF), may be useful to detect patients with grade 1 HE but may fail to detect patients with MHE.³⁶ This was also proved by the poorer prognosis of patients with altered CFF than patients with normal CFF vs. patients already having altered psychometric performance.³⁷ Quantified electroencephalogram, which is independent of patient cooperation and has a good prognostic value,³⁸ can detect different levels of brain suffering, but its use is limited until friendly equipment and quantifying procedures will be cheap and easily available.

The time course is relevant because the risk of future bouts of overt HE is higher in patients who had two bouts (~40%) than in those who had only one bout of HE (~25%) in the previous 6 months.^{39,40} Furthermore, the latter have higher risk than those who did not have previous bouts of HE (9–35% in 5 years).^{40–42} Of note, the interval of 6 months was arbitrarily defined because no study proved that this is the optimal one, but it is reasonable that it is a good compromise between a too short interval in which the likelihood of a bout of overt HE is low and a too long interval in which the information about bouts of overt HE might be lost. At any rate, the qualification of HE concerning its time course is of fundamental importance because secondary prophylaxis is mandatory in subjects who had previous bouts of HE, and current consensus gives different suggestions depending on the frequency of recurrence.¹¹

Precipitating factors should be mentioned because *i*) the occurrence of recognized precipitating factors increases the likelihood of proper diagnosis and *ii*) attention can be focused to prevent the recurrence of a specific precipitating factor. For instance, if the precipitating factor is constipation, treatment and education oriented to avoid constipation will be important, and if the precipitating factor is gastrointestinal bleeding, measures to avoid bleeding will be important, etc.

The AASLD/EASL practice guidelines do not affirm the opportunity to report the response to ammonia-lowering treatments (disaccharides, oral antibiotic, L-Ornithine-L-Aspartate (LOLA), nonureic nitrogen-wasting products). At any rate, this information is useful both to confirm the diagnosis and to guide treatment, and thus, it should be added. The resulting classification grid is reported in Table 4.

CONFLICTS OF INTEREST

The author has none to declare.

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