

Lights and shadows in hepatic encephalopathy diagnosis

Piero Amodio ^{1*} and Sara Montagnese ¹

¹ Department of Internal Medicine -DIMED- Università di Padova; piero.amodio@unipd.it

¹ Department of Internal Medicine -DIMED- Università di Padova; sara.montagnese@unipd.it

Correspondence: Piero Amodio, MD, FRCP; piero.amodio@unipd.it; Tel.: **390397801153

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Abstract: Hepatic encephalopathy (HE) is a form of brain dysfunction that is specifically caused by liver insufficiency and/or portal-systemic shunt. The exact nature of HE is debated, so that conflicting uses of the term HE may cause inconsistencies in its detection and, in turn, issues with its management. This review highlights the meaning of the term HE on the basis of both its historical origins and current consensus. It also provides criteria for the diagnosis of the condition, on the basis of its phenotypes and the risk factors for its occurrence. The procedure for differential diagnosis from other conditions which result in similar phenotypes is considered, together with precipitants and confounders. Finally, the current multidimensional approach for the correct clinical recording of HE episodes is discussed.

Keywords: liver failure 1; encephalopathy 2; delirium 3; coma 4; cirrhosis 5;

1. Introduction

The diagnosis of hepatic encephalopathy (HE) is relevant, because HE is a marker of poor survival in cirrhosis and ALF (1,2), and is a disabling condition resulting in poor quality of life in patients and their caregivers (3). Further, HE causes relevant direct costs to the health systems (4), also because it is the second cause of hospitalization in patients with cirrhosis and the first cause of re-hospitalization (5). It causes also indirect costs related to patient's and caregiver's work loss (6). A correct diagnosis is required to select proper treatment, to prevent further episodes in single patients and to conduct meaningful prevention/treatment trials.

Despite the fact that the diagnosis of HE may seem a simple one, and frequently this is the case, on closer inspection the item is not as trivial as it may appear and depends on what we consider to be HE, i.e. on its definition.

2. The meaning of the term HE

The recognition of an association between jaundice and behavioural alterations is very ancient, the one between cirrhosis and confusion/stupor about three centuries-old, while the pathophysiological explanation of such associations dates back to end of the nineteenth century (7). On this basis the AASLD/EASL practice guidelines for HE defined HE as *“Brain dysfunction caused by liver failure and/or portal-systemic shunt (PSS); it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical*

alterations to coma" (8). The adjective "hepatic" is used to underline a pathophysiological link with liver failure and/or portal-systemic shunt. However, some authors (9) have used the adjective "*hepatic*" to simply indicate an encephalopathy of undefined aetiology in patients with liver disease. However, this is criticisable, since never in medicine an encephalopathy is qualified based on the disease in which it occurs. By contrast, it is qualified based on the mechanism causing encephalopathy/delirium. Thus, the terms "*lung encephalopathy*" or "*cardiac encephalopathy*" do not exist while the terms "*hypercapnic encephalopathy*", "*hypoxemic encephalopathy*" and "*cerebral hypoperfusion encephalopathy*" are those used. Thus, if the term "*hepatic*" does not refer to a specific mechanism, it is better replaced by one referring to one (i.e. "patient with cirrhosis and benzodiazepine intoxication", or "opioids overdose", or "hyponatraemic encephalopathy", "septic encephalopathy", "hyperammonaemia" and so on). This avoids misinterpretation and malpractice derived by the use of the same treatment for conditions with different underlying pathophysiology. For an analogy, using the term hepatic encephalopathy this way and treating the syndrome accordingly would be the same as treating fever in patients with liver cirrhosis under the heading of "hepatic fever", regardless of its cause (i.e. pneumonia, urinary tract infection, spontaneous bacterial peritonitis etc.). By contrast, the idea that in patients with cirrhosis encephalopathies should be classified and managed depending on their aetiology was clearly formulated by Riddell about 65 years ago (10): '*... 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*'.

Considering the definition given by the AASLD/EASL practice guidelines, the question may arise: "*Which is brain dysfunction caused by liver failure and/or PSS?*" This question implies the detection of a mechanism that *specifically* links these conditions. Such link between a failing liver and/or PSS and encephalopathy concerns abnormalities in nitrogen metabolism, because the liver has a unique role in the detoxification of ammonia, and most other substances coming from the gut. This was proved by the observation that dogs undergoing portal-caval shunt: *i)* develop encephalopathy after the consumption of ammonia salts and nitrogen containing-foods, *ii)* reduce their urinary urea excretion, *iii)* reduce their capacity to synthesize urea from gastric-infused carbamic acid (11). Further, the oral administration of ammonium chloride to cirrhotic patients causes coma (12), and the toxicity of ammonia on the human brain is proved by cognitive defects concerning attention/executive function and coma in individuals with hereditary defects of urea cycle enzymes (13). Finally, the creation of large portal-systemic shunts causes hyperammonaemia and encephalopathy in humans, and their obliteration reduces ammoniaemia and improves HE (14).

Obviously, PSS and hepatic failure may cause the increase in any neurotoxic substance originating from the gut that has a high first-pass hepatic metabolism, like ammonia. Research on this has been limited over the past years, after the emphasis given to the topic by Zieve (15). Substances with the above features which may have a pathophysiological role in

HE are: *i*) manganese - particularly in the motor disturbances associated with HE - since it deposits in the basal ganglia because of its reduced clearance in portal-systemic shunt and cholestasis (16), and *ii*) indole, that crosses blood brain barrier and produces oxindole within the brain, which is a neurotoxic substance (17). Further, gut dysbiosis, Kupffer cell dysfunction (18) and portal-systemic shunt may favor systemic inflammation, which also affects brain function (19,20).

HE in acute liver failure is a distinct type of HE that occurs in the context of severe cytokine storm and brain as well systemic hemodynamic alteration (21,22); thus, it has separate features in which brain swelling and intracranial hypertension have a peculiar role, thus it is a distinct condition with respect of HE occurring in cirrhosis and in non-cirrhotic portal systemic shunts (8).

Recently it has been observed that HE in acute on chronic liver failure has some peculiar features (23,24). It frequently occurs in the context of multiorgan failure, sepsis and cytokine storm that reasonably produce overlapping metabolic/haemodynamic encephalopathies that may deserve to be considered separately and frequently require multitarget treatment in ICU managed patients.

At any rate, in all cases of suspected HE, especially in the context of ALF or ACLF, the exclusion of alternative causes of severe brain dysfunction is mandatory, because of the implications that a wrong or missed diagnosis can have in severely ill patients

3. The Diagnosis of HE

The diagnosis of HE, as every clinical diagnosis, results from the *a priori* probability of HE before any observation, and the probability that a clinical finding relates to HE. This should be compared with the probability of alternative conditions.

Thus, the degree of certainty for the diagnosis of HE depends on three key steps: *i*) the *a priori* probability of HE, *ii*) the recognition of a clinical pattern suggestive of HE (Table 1), *iii*) the consideration of alternative conditions.

In formal Bayesian terms:

Odds of HE = a priori Odds of HE prevalence *x* *Positive Likelihood Ratio of clinical findings for HE*
vs. a priori Odds of alternative condition prevalence X Positive Likelihood ratio of clinical findings for alternative conditions.

Table 1: The phenotypes by which HE may appear to clinical observation

Pattern		Description
A) Coma		Eyes closed; patient is unresponsive even to pain stimulation.
B) Rapidly developing confusional state	Inhibited	The patient is disoriented for time and/or space and/or identity (to varying degree) and is somnolent/stuporous. Asterixis is usually detectable.
	Agitated	The patient is disoriented for time and/or space and/or identity and agitated/nervous/restless.
C) Almost continuous mild mental dysfunction with interspersed recurrent episodes of more severe confusion		The pattern is dementia-like; asterixis is usually detectable.
D) Predominant motor disorder with mild/moderate mental dysfunction/confusion	Extrapyramidal	Parkinsonism, chorea or athetosis. Asterixis is usually detectable.
	Pyramidal	Spastic paraparesis with hyperreflexia. Asterixis is usually detectable.
E) Mild brain dysfunction		The patient is oriented for time and space and his/her mental activity seems normal/near-normal; however, caregivers or health personnel may recognize a decay from the patient's standard in terms of behavior, irritability and cognition. On psychometric testing, alterations are detectable (in attention, working memory, cognitive speed and inhibition). Other signs, associated or independent of psychometric alterations, include slowed electronecephalographic activity and/or reduced critical flicker frequency. Dissociations between findings on different techniques is common.

The *a priori* probability of HE depends on the severity of liver failure (25,26) and/or the extent of PSS (27), plus the history of previous episodes of overt HE (28). Of note, the severity of liver failure and large PSS have a fundamental role, and they are associated with

high levels of plasma ammonia, which is a known risk factor for HE (29,30). Thus, the *a priori* probability of HE for subjects with normal/low levels of plasma ammonia is low, if any, considering also the specific role of nitrogen metabolism abnormalities in the pathophysiology of HE.

The *a priori* probability is also increased by the occurrence of precipitating factors for HE (Table 2).

Table 2. Prevalence (percentage) of the main precipitating factors for hepatic encephalopathy (HE), modified from Strauss et al. (31)

		Episodic HE	Recurrent HE
Infections		33	26
	<i>Spontaneous bacterial peritonitis</i>	11	5
	<i>Urinary</i>	7	12
	<i>Respiratory</i>	5	5
	<i>Sepsis (unknown)</i>	8	2
	<i>Skin</i>	2	2
Bleeding		30	4
Dehydration/ hypovolaemia/ hyponatraemia		24	5
Constipation		0	5
Not recognised		2	26

Note: Subsequent papers report comparable values, with the exception of a reduced role of bleeding, probably due to improvement in bleeding prevention. Of note, the higher prevalence of unrecognised precipitants for recurrent HE highlights the high vulnerability of these individuals so that minimal metabolic disturbance can induce HE.

Precipitating factors are those which intervene in the pathophysiology of HE, increasing the production of ammonia or its neurotoxicity. For instance, gastrointestinal bleeding and constipation increase ammonia production, inflammation (especially that associated with infection) and hyponatremia increase ammonia toxicity (28,32,33). Further, infection increases also ammonia production (13), as well as hypothyroidism that is both a confounder and a precipitant for HE (34), so that thyroid function should be investigated and corrected, if required.

Thus, they should be differentiated by additional or confounding factors of brain dysfunction which impair brain function by other mechanisms (Table 3).

Table 3. Differential diagnosis of HE, depending on the phenotype

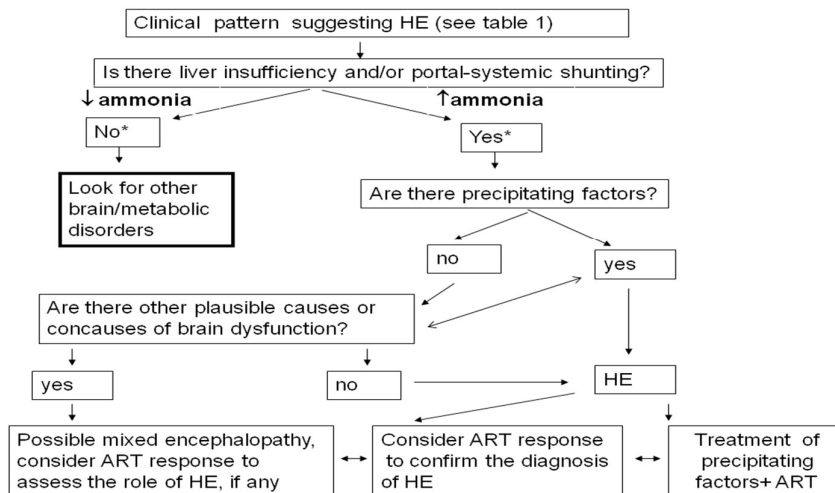
Phenotype	Alternative or concurrent causes of the phenotypes of HE
A/B	<ol style="list-style-type: none"> 1. Encephalitis/meningitis, diabetic ketoacidosis or hyperosmolar coma 2. Drug intoxication (benzodiazepines, opioids, neuroleptics, valproate, antiepileptic drugs or quinolones) or alcohol intoxication 3. Head trauma 4. Hypercalcaemia 5. Hypercapnia 6. Hypoglycaemia (coma) 7. Non-convulsive epilepsy (coma) 8. Psychosis 9. Sepsis* 10. Severe acute hyponatremia* 11. Stroke (haemorrhagic/ischemic) 12. Wernike's encephalopathy (thiamine deficiency) (confusion) 13. Malingering
C	<ol style="list-style-type: none"> 1. Alcohol-related dementia 2. Neurodegenerative dementias 3. Brain masses (subdural hematoma, low growing tumors) 4. Hypercalcaemia 5. Hyponatraemia* 6. Hypothyroidism 7. Korsakoff dementia (thymine deficiency) and other micronutrient deficiencies (e.g., B₁₂) 8. Neurological sequelae of head trauma 9. Renal failure (uremic encephalopathy/dialysis and disequilibrium syndrome) 10. Vascular dementia <ol style="list-style-type: none"> a. Binswanger disease (subcortical dementia) b. Hypoperfusion c. Large stroke or multiple strokes d. Stroke in strategic areas
D	<ol style="list-style-type: none"> 1. Cerebrovascular disorders 2. Dementia with Parkinsonism 3. Normotensive hydrocephalus 4. Extrapyrarnidal syndromes 5. Demyelinating disorders 6. Vitamin B₁₂ deficiency 7. Wilson disease
E	<ol style="list-style-type: none"> 1. Every cause of non-amnestic mild cognitive impairment; of note, obstructive apnoea syndrome,

Of note, mixed encephalopathies are possible and it is obvious that the addition of other factors for brain dysfunction to HE facilitates the occurrence of delirium. In case of a mixed encephalopathy the treatment of the amount of brain dysfunction caused by HE may improve, but not completely revert the clinical picture (35).

It should be considered that the distinction between precipitating and confounding factor is not always simple or clear cut, since some factors can alter brain function *per se*, also in patients without liver failure, but also intervene in the mechanisms of ammonia toxicity. For example, septic encephalopathy, hyponatremia can alter brain function *per se*, independently of liver failure but when occurring within the context of liver failure or PSS they facilitate the occurrence of HE, most likely in addition to their specific, respective neurotoxic mechanisms. A schema that summarizes the diagnostic process is reported in figure 1.

In addition to the issue if there is HE -and, thus, *what is HE and what is not HE-*, the diagnosis of HE requires some additional attributes, concerning its type, severity, rate of recurrence, precipitants factors and facilitating factors (36). Thus, a complete diagnosis should be multidimensional, as it has been emphasized in the practice guidelines of the AASLD/EASL (8) and the AIFS (36) (fig. 2).

4 Figures



ART= ammonia reducing treatment (non-absorbable antibiotic +/- disaccharides)

Figure 1. Flow chart for the diagnosis of HE (modified from (37)).

Type	Severity	Time course	Facilitating and precipitating factors	Ammonia lowering agents
A Acute liver failure	Quantification/neuromonitoring is closely linked to the expertise of ICUs caring for the patients			
B Portal-systemic shunt (no significant liver disease)		episodic recurrent (≥2 bouts OHE in 6 mo) persistent (dementia or dementia-like)	No/Yes (possibly report the precipitant factor)	No/Yes (for all conditions)
C Liver cirrhosis (both liver failure and portal-systemic shunt)				
D Acute on Chronic Liver Failure	<i>Research area</i> <i>Different management, mechanism, and prognostic impact</i>			

Figure 2. Multidimensional schema for the diagnosis of HE, following the AISF practice guidelines for HE, from (36)

5. Conclusions

The existence of poor liver failure, PSS, prior HE, precipitating factors increase the *a priori* probability of HE. The exact quantification of the OR provided by these conditions and quantification of their interaction is lacking. They only confer a subjective degree of confidence about the *a priori* likelihood for the diagnosis.

Another milestone for the diagnosis depends on the recognition of the phenotype of HE (37), none of which is specific. Thus, alternative or concurrent conditions should be considered particularly for the patterns where a rapid alternative diagnosis may have clinical relevance, such as coma, or when the pattern is not frequent in HE, such as when the picture is mainly motor or when there is sub-continuous, fluctuating mental dysfunction. In practice, in most cases the diagnosis is simple, in particular when there is strong *a priori* probability, the patient has only liver disease and the phenotype is the one of confusion. In other situations, the diagnosis can be more difficult. It is reasonable to assume that HE is confirmed if a full dose regime of non-absorbable disaccharides and non-absorbable oral antibiotics, that significantly reduce plasma ammonia, improves or completely reverts symptoms in a few days. Finally, after having reach a correct diagnosis of the existence of HE, multidimensional

qualification is required to characterize the type, the severity, the time course, precipitant/favoring factors.

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