Definition and Nomenclature of Hepatic Encephalopathy

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Hepatic encephalopathy (HE) can manifest with a broad range of neuropsychiatric abnormalities of varying severity, acuity and time course with significant clinical implications. Lack of precise nomenclature and classification had hampered research in this complex clinical problem. A multiaxial classification system based on underlying etiology, clinical severity, time course and presence or absence of precipitating factors has been developed over the recent years and has been fully incorporated in the newly published AASLD-EASL guidelines on HE management. This multiaxial classification is expected to bring uniformity in describing and categorizing of HE across centers and nations, foster clinical research and improve patient care and outcome. (J CLIN EXP HEPATOL 2014;5:S37–S41)

According to the new American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guideline, HE is defined as “brain dysfunction caused by liver insufficiency and/or portosystemic shunting, and manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma” (AASLD-EASL guideline, Hepatology 2014 In Press).¹

CLINICAL IMPACT

The neuropsychiatric impairment associated with HE can range from subtle, mild alteration of cognition and consciousness to coma, to severe neurodegeneration depending on the stage of the illness. In general, the neuropsychiatric impairments associated with HE are largely reversible. However, complete regeneration and restoration of the brain functions may not be possible in the extreme cases of severe hepatocerebral degeneration.

HE is one of the most debilitating manifestations of liver cirrhosis with profound impact in the quality of lives of patients and their caregivers. HE remains a major challenge in clinical management of patients with liver disease as only little is understood of its complex pathogenesis.

Moreover, there is lack of universally acceptable standardized definition, nomenclature and classification further hindering research and clinical care of patients affected by HE. More recently, however, significant progress has been made in recognizing the magnitude of this problem. As a result, the field of HE is rapidly evolving with constant updates in its nomenclature and classification.

NOMENCLATURE & CLASSIFICATION

Until fairly recently, there had been no consensus on the diagnostic criteria and thus existed a great deal of confusions regarding the nomenclature and classification of HE. Much of this was resolved after the first consensus conference in this regard held during the 11th World Congress of Gastroenterology in Vienna in 1998 which published its consensus multiaxial definition and classification of HE in 2002.^{2,3} Despite this, the topic of classification and nomenclature of HE continued to remain a subject of ongoing debate and modifications. In 2011, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN)⁴ released its consensus statement outlining the proposed classification and nomenclature of HE. The main aim of the consensus was to review the current classification of and to develop consensus guideline on the design and conduct of future clinical trials. This has led to a more practical, descriptive classification system with implications in clinical care and research trials of patients with HE. The AASLD-EASL joint working group have just put together their guideline¹ on the management HE associated with chronic liver disease. This guideline in essence encompasses the nomenclature and classification system originally proposed by ISHEN and recommends that all HE should be categorized based on following four axes: underlying etiology, clinical severity, time course, and presence or absence

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Abbreviations: HE: hepatic encephalopathy; SONIC: spectrum of neurocognitive impairment in cirrhosis

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of precipitating factors. This multiaxial classification and nomenclature is expected to bring uniformity in describing and categorizing of HE across centers and nations, foster clinical research and improve patient care and outcome.

The clinical diagnosis of overt HE is based on the combination of mental status abnormalities and impairment of neuromotor functions such as asterixis, hyperreflexia and hypertonicity and can only be established after exclusion of other causes of altered mental status. The mental status abnormalities of HE is classically graded by the West Haven criteria which categorizes HE from grade I to grade IV based on various clinical parameters such as alteration in the level of consciousness, intellectual function and behavior, and presence or absence of asterixis (Table 1).⁵ The West Haven scale is however, criticized for its subjectivity, and extreme intra- and inter-observer variability, particularly in identifying patients in Grade I category.^{4,6} This is partly because this scale was meant to be a semi-quantitative method and co-opting it as a “gold-standard” has led to issues in interpretation, especially in the earlier stages. Studies have shown that the reliable presence of overt HE can be minimized by using ‘disorientation to time’ as a criterion for Grade II HE.^{7,8} Therefore the diagnosis of overt HE at grade II and higher severity has good inter-rater and inter-site reliability.

Overt Hepatic Encephalopathy, Minimal Hepatic Encephalopathy, and Covert Hepatic Encephalopathy

The clinically apparent forms of HE are generally described as **overt HE**. Overt HE consists of neuropsychiatric abnormalities that can be detected by bedside clinical tests. Overt HE can encompass a wide spectrum of mental and motor disorders and may arise episodically over a period of hours of days in a patient who had previously been in a stable

mental state or less commonly, as persistent neuropsychiatric impairment that will remain stable for a period of time.^{4,6} Overt HE can be further classified in to grade II, III or IV HE based on the clinical features as originally outlined in the West Haven criteria. As mentioned above, grade I is difficult to generalize across sites, since it requires a knowledge of the patients.

The term ‘**minimal HE**’ was coined to refer to the subtle subclinical impairment of cognition that is not apparent clinically and can only be detected by specific psychometric or neurophysiologic tests, replacing the older term “subclinical HE”.² Since its introduction as a distinct type of HE in the classification, there has been significant advancement in our understanding of minimal HE. Despite absence of any clinically apparent signs or symptoms, minimal HE has been clearly shown to impact the quality of life of patient with chronic liver disease tremendously.⁹ Minimal HE is associated with reduced ability to perform complex tasks such as driving^{10,11} and reduced ability to hold certain kinds of employment. Most importantly, minimal HE predicts future onset of overt HE.¹²

Because of the difficulty in diagnosing overt HE if grade I is also included, the ISHEN 2011 guideline introduced the term “covert HE” to include grade I and minimal HE as an umbrella term to ease reliability of patient inclusions into multi-center clinical trials.⁴ Any patient with subtle mental changes but who is ‘disoriented’ and/or has ‘asterixis’ will meet criteria for grade II HE and therefore should be categorized as overt HE as opposed to covert HE. By definition, covert HE will refer to the psychometric or neurophysiological abnormalities in the absence of disorientation and asterixis and will include West Haven Grade I HE and minimal HE. This distinction is of particular importance in designing and conducting clinical trials. Studies show that covert HE is a multifactorial group which requires future validation and study.¹³

The process of neurocognitive dysfunctions leading to HE appears to be a dynamic, continuous process that constantly move from one state to another rather than staying in to discrete separate entities. This evolving concept of continuum is also defined as the ‘spectrum of neurocognitive impairment in cirrhosis (SONIC)’¹⁴ and continues to draw considerable interest to the researchers in this field.

NOMENCLATURE UPDATES IN THE 2014 AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES/EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER GUIDELINES: THE FOUR AXES

Very recently, AASLD and EASL have come up with joint guideline for the management of HE in chronic liver disease. Following review of the current evidence and reassessment of existing classifications, the task force recommends that HE should be classified based on the

Table 1 West Haven Criteria of Grading Mental State in Patients with Cirrhosis (Adapted from Conn H0).⁵

Grade	Features
0	No abnormalities detected
I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction
II	Lethargy or apathy Disorientation to time Obvious personality change Inappropriate behavior
III	Somnolence to semi-stupor Responsive to stimuli Confused Gross disorientation Bizarre behavior
IV	Coma Unable to test mental state

underlying etiology, severity of clinical manifestations, time course and whether or not a precipitating factor is identified (Table 2).¹

It should be noted that this nomenclature system primarily pertains to HE associated with chronic liver diseases (i.e., type C based on Vienna classification).² None the less, this system of description can be applied to HE associated with acute liver failure (type A) or related to portosystemic shunting from various etiologies (type B).

Each of these four axes bears unique importance in the clinical description, management, and prognosis of patients with HE.

Axis 1: Etiology

It is clear that the prognosis of HE can be very different based on the underlying etiology. So can be its management. For instance, HE associated with acute liver failure can progress very rapidly and may lead to brain herniation with devastating consequences if not dealt in time and properly. Also, the management and long term prospects are distinct from HE resulting from cirrhosis. Likewise, an overtly encephalopathic patient without clinically apparent etiology may have had spontaneous portosystemic shunting. High quality imaging may be able to detect such shunt, and shunt closure with intervention can lead to complete reversal of encephalopathy and such patient may return to normal life.

Based on etiology, HE is classified in to 3 'types':

- **Type A:** due to acute liver failure
- **Type B:** due predominantly to portosystemic shunting or bypass
- **Type C:** due to cirrhosis

While the clinical manifestations and management of type B and type C HE are generally similar, HE associated with acute liver failure has a distinct underlying pathology and can be associated with increased intracranial pressure and can lead to cerebral herniation. Type A HE should be

managed according to the acute liver failure guidelines (AASLD ALF guideline).¹⁵

Axis II: Clinical Severity

It is important to recognize and correctly identify the severity (or the grade) of encephalopathy so that appropriate level of care, therapy and monitoring is provided to these patients. Patients with minimal HE do not have current standard of care treatments. On the other hand, patients with grade III HE may be at risk of aspiration and or coma and will need active vigilance and support. Also, it is imperative that the clinical trials across centers enroll patients with similar grade of severity so that the outcome can be interpreted more meaningfully and applied in the care of the right set of patient populations.

Based on severity, HE should be classified into the following 'grades' (Table 2):

- Unimpaired (normal, no subclinical or clinical impairment of mental state)
- Minimal (abnormal specialized tests but normal mental status)
- West Haven Grades I through IV

With the guidelines, the updated grades of HE would be further classified into covert and overt as follows:

- Unimpaired
- Covert HE: includes minimal HE (Vienna definition) + West Haven Grade I (absence of disorientation and asterix).
- Overt HE: includes West Haven Grade II-IV HE and needs to be further specified to grade II, III, or IV

Persons with normal mental status are labeled as unimpaired. While the distinction between minimal HE and grade I HE may not be clinically apparent (detection of minimal HE generally requires specialized psychometric and/or neurophysiological tests), distinction between grade I and grade II is of great clinical importance. Any person with evidence of any disorientation or asterix will have grade II HE, with significant impact on their quality of life and will require treatment whereas covert HE (minimal HE and grade I HE) could potentially be monitored without therapy.

Axis III: Time Course

Knowledge of the clinical course and progress in the context of time may be useful in determining prognosis, setting goals of long term care, allocations of resources and treatments, both for the care givers and care providers. Also, it may be possible to stop treatment in someone with single episode of HE with prolong period of normalcy, especially if the HE event was a precipitated by a correctable event. This is not applicable for MHE/CHE since their clinical course is not clear.

Table 2 Clinical Description of Hepatic Encephalopathy (Adapted from AASLD-EASL Guideline 2014).¹

Type	Grade		Time course	Spontaneous/precipitated
A	Minimal	Covert	Episodic	Spontaneous
B	I		Recurrent	Precipitated (specify)
C	II	Overt	Persistent	
	III			
	IV			

Each episode of HE should be characterized by one component from each of the 4 axes or columns. Also, covert HE should be further characterized as grade II, III or IV.

For example: HE, Type C, Covert, Grade III, Episodic, Precipitated by dehydration.

Based on time course, HE can be

- **Episodic:** bouts occurring more than 6 months apart
- **Recurrent:** bouts recurring within a time frame of 6 months or earlier
- **Persistent:** patterns of behavioral alterations that are always present interspersed with relapses of overt HE

Axis IV: Precipitated or Spontaneous

This axis aims to emphasize the importance of evaluation and management of the precipitating factors. A precipitating factor or event should be sought for with every instance of overt HE, and should be corrected whenever possible. Recurrent and worsening HE in the absence of a precipitating factor may indicate progression of the underlying liver disease and poor prognosis. This is again not applicable for MHE/CHE since their clinical course is not clear.

Based on presence of absence of detectable precipitating factor, HE can be

- **Spontaneous** (non precipitated)
- **Precipitated** (secondary to)

The proper description of all overt HE episodes should include the all four of the above criteria.

Examples:

- 1) A 56 year old male with chronic hepatitis C presents to the hepatitis clinic to discuss treatment options. He was found to have cirrhosis on a recent liver biopsy. His liver function tests are all within normal. He is currently working as a post man and in fact, drove himself to the clinic. His physical examination was normal and he did not have asterixis. He was oriented to time, place and person. Owing to the high risks of any potential cognitive impairment, he was asked to undergo a battery of neuropsychiatric and psychometric test in the local HE research lab. He failed those tests and was diagnosed to have minimal HE. He will be followed in the clinic closely for any overt HE.

Based on the current recommendations, this will be classified as:

Type C, minimal.

- 2) A 60 year old female in the liver transplant wait list is admitted for the 3rd time in a month with acute mental confusions. She is already on lactulose and rifaximin and her caregivers maintain patient's compliance. Patient is disoriented to time and place, but has no focal neurological deficits. Lab work up was notable for gross pyuria. She was treated with a course of antibiotics and got better and was discharged home

Based on the current recommendations, this will be classified as:

Type C, overt Grade III, recurrent, precipitated by urinary tract infection.

- 3) A 55 year old male teacher with a diagnosis of nonalcoholic steatohepatitis had been admitted to hospital multiple times over the past 6 months with recurrent episodes of confusion. Head CT has been normal. Routine labs including liver function tests are normal except high ammonia of 100 $\mu\text{g/dL}$. Serum and urine toxicology screens are negative. Chest X-ray is normal, and has normal urinalysis and negative blood cultures. He does not have a history of jaundice, ascites, edema or gastroesophageal varices. Prior abdominal imagings have been normal except for parenchymal liver disease. A recent liver biopsy showed bridging fibrosis. A high resolution multi slice CT abdomen was performed which shows spontaneous splenorenal shunt.

This gentleman happens to have: **Type B, overt, grade III, recurrent HE, non-precipitated.** Such patient may benefit for shunt closure.

- 4) A 22 year old female with no prior medical history has been admitted to the intensive care unit with inadvertent overdose with acetaminophen. She is being monitored closely and is getting N-acetylcystine therapy. She was fully alert and oriented to time, place and person at presentation, and within several hours, she becomes progressively drowsy, slow and is intubated for airway protection. Head CT was normal. Her lab work up is otherwise unremarkable except for highly elevated transaminases and INR of 1.6.

This patient has an encephalopathic episode related to acute liver failure. This should be classified as:

HE: Type A, Overt, grade IV, episodic, non-precipitated.

- 5) A 47 year old man with chronic alcoholic cirrhosis who has been abstinent for more than 3 years was brought to clinic by his mother who claims that he is a "little bit slower than usual". On examination, he does not have ascites, asterixis and is oriented to time, place and person. Since you have been seeing this patient for more than 3 years, you also agree with the mother that "something is not right". On investigation, no signs of infection, changes in underlying liver function or addition of new medications are found. The cognitive tests performed show significant impairment in all fields tested.

This would qualify as grade I in the West Haven criteria but this is only apparent because the patient is well-known to everyone concerned who can identify issues with them readily but would potentially be missed or misclassified in multi-center studies.

Based on current recommendations, this would be HE: Type C, covert.

- 6) A 65 year old male with hepatitis C related cirrhosis presents to the liver clinic for a scheduled follow up. His course has been complicated by refractory ascites

requiring serial large volume paracentesis and encephalopathy. Rifaximin was recently added to his regimen as he continued to remain confused and forgetful despite lactulose therapy with 3–4 loose stools a day. Today, he reports to be doing fine overall. He appears slow and has asterixis. His wife reports he is taking all his medications as prescribed. There has been no recent fever, chills. His labs including comprehensive metabolic panel, urinalysis, and toxicology screen are all within normal.

He appears to have: **Type C, Overt, grade II, persistent HE, non-precipitated.**

SUMMARY

In summary, the nomenclature and classification of hepatic encephalopathy continues to evolve as our understanding of this complex neuropsychiatric process advances. For practical purposes, HE should be categorized based on the underlying etiology, clinical severity, time course and precipitating factors as recommended by the recent AASLD-EASL guidelines. This four axis descriptive classification system is expected to improve description and categorization of the diagnosis, bring more uniformity in research and clinical trials across centers and continents, and improve quality of care and outcomes among patients with HE.

CONFLICTS OF INTEREST

All authors have none to declare.

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