SPECIAL ARTICLE

Hepatic Encephalopathy—Definition, Nomenclature, Diagnosis, and Quantification: Final Report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna, 1998

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Research on hepatic encephalopathy is hampered by the imprecise definition of this disabling complication of liver disease. Under this light, the Organisation Mondiale de Gastroentérologie commissioned a Working Party to reach a consensus in this area and to present it at the 11th World Congress of Gastroenterology in Vienna (1998). The Working Party continued its work thereafter and now present their final report. In summary, the Working Party has suggested a modification of current nomenclature for clinical diagnosis of hepatic encephalopathy; proposed guidelines for the performance of future clinical trials in hepatic encephalopathy; and felt the need for a large study to redefine neuropsychiatric abnormalities in liver disease, which would allow the diagnosis of minimal (subclinical) encephalopathy to be made on firm statistical grounds. In the interim, it proposes the use of a psychometric hepatic encephalopathy score, based on the result of 5 neuropsychologic tests. Finally, the need for a careful evaluation of the newer neuroimaging modalities for the diagnosis of hepatic encephalopathy was stressed. (HEPATOLOGY 2002;35:716-721.)

Hepatic encephalopathy (HE) continues to be a major clinical problem. In subjects with acute liver failure, patients can succumb to a neurologic death, with brain edema and intracranial hypertension.[1] In patients with cirrhosis, the Child classification recognizes the prognostic significance of HE.[2] The current decade has not witnessed major therapeutic breakthroughs in this area. However, there is a need to delineate better research tools in preparation for new developments, and define mild forms of the disorder and their response to treatment. Drugs that work directly on the brain will become increasingly available for clinical testing. The current epidemic of hepatitis C is increasing the number of patients with cirrhosis and raising questions about alterations in biological functions, such as sleep and appetite, that are intertwined with the significance and pathogenesis of minimal (subclinical) encephalopathy.

Under this light, the Organisation Mondiale de Gastroentérologie commissioned a Working Party to reach a consensus in this area and to present it at the 11th World Congress of Gastroenterology (WCOG) in Vienna (1998). The study of the changes in mental state in patients with liver disease requires the expertise of several disciplines, including hepatology, neurology, and neuropsychology, all represented in the composition of the Working Party. Four questions were tackled:

1. Is there a need for a standardized nomenclature? If so, what terms could become acceptable for general use? (Discussion led by Dr. Kevin Mullen.)
2. What are the best outcome measures to report efficacy in clinical trials? (Discussion led by Dr. Peter Ferenci.)
3. What constitutes minimal (subclinical) encephalopathy in patients with cirrhosis? (Discussion led by Dr. Ralph Tarter.)

Abbreviations: HE, hepatic encephalopathy; WCOG, World Congress of Gastroenterology; EEG, electroencephalogram; NCT, number connection test; TIPS, transjugular portal-systemic shunt; PET, positron emission tomography.

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4. What is the role of current neuroimaging techniques for the diagnosis of HE? (Discussion led by Dr. Alan Lockwood.)

Subsequent to the WCOG, several further meetings were held at the 10th International Symposium on Ammonia (Istanbul, Turkey, May 1999) and the Annual meetings of AASLD in 1999 and 2000 (Dallas, TX). The final document was written after these further discussions and circulated among the members of the Working Party.

Is There a Need for a Standardized Nomenclature? If so, What Terms Could Become Acceptable for General Use?

Background

Surveys performed before the WCOG meeting among attendees to meetings on HE showed considerable discrepancy on the terms used to define different clinical settings. Major points of controversy included:

- The term "portal-systemic encephalopathy" is widely used and reflects the influence of portal-systemic shunts on the development of changes in mental state. However, such shunts can also exist without intrinsic liver disease, and the contribution of shunting to the abnormal mental state is difficult to separate from the presence of intrahepatic abnormalities in the patient with cirrhosis.
- The term "acute encephalopathy" was interpreted by some as indicating the encephalopathy of acute liver failure, whereas for others, it meant the presence of a reversible episode in patients with cirrhosis.
- The term "chronic encephalopathy" was used to describe both patients with recurrent episodes of encephalopathy as well as subjects with continuous abnormalities of the mental state.

A standard nomenclature would provide a solution to this debate, as well as normalize the performance of clinical studies and therapeutic trials in HE.

Consensus Statement

HE reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease. A multiaxial definition of HE is required that defines both the type of hepatic abnormality and the duration/characteristics of neurologic manifestations in chronic liver disease (Table 1).

The Type of Hepatic Abnormality.

- Encephalopathy associated with acute liver failure. *Alternative term*: type A (for acute liver failure).
- Encephalopathy associated with portal-systemic bypass and no intrinsic hepatocellular disease. *Alternative term*: type B (for bypass).
- Encephalopathy associated with cirrhosis and portal hypertension/or portal-systemic shunts. *Alternative term*: type C encephalopathy (for cirrhosis).

Duration/Characteristics of Neurologic Manifestations in Chronic Liver Disease. *Episodic HE.* In the DMS-IV classification system, this corresponds to a "Delirium due to a General Medical Condition (code 293.0)." Delirium is defined as "a disturbance of consciousness that is accompanied by a change in cognition that cannot be better accounted for by a pre-existing or evolving dementia," that develops over a short period of time and fluctuates in severity.[3]

Table 1. Proposed Nomenclature of HE

HE Type	Nomenclature	Subcategory	Subdivisions
A	Encephalopathy associated with **a**cute liver failure		
B	Encephalopathy associated with portal-systemic **b**ypass and no intrinsic hepatocellular disease.		
C	Encephalopathy associated with **c**irrhosis and portal hypertension/or portal-systemic shunts	Episodic HE	Precipitated Spontaneous* Recurrent
		Persistent HE	Mild Severe Treatment-dependent
		Minimal HE	

NOTE. For definitions see text.
*Without recognized precipitating factors.

It is further divided into HE episodes with (precipitated) or without recognized precipitating factors (spontaneous). Before the term "spontaneous" is used, precipitating factors should be excluded: gastrointestinal hemorrhage, uremia, use of psychoactive medication or of diuretics increasing renal ammonia release, dietary indiscretion, infection, constipation, dehydration, hypo- or hyperkalemia, and hyponatriemia. "Recurrent encephalopathy" is a term used when 2 episodes of episodic HE occur within 1 year.

Persistent HE. This includes cognitive deficits that impact negatively on social and occupational functioning. Persistent noncognitive abnormalities (such as extrapyramidal alterations or sleep disturbances) require separate tabulation.

It is further subdivided into mild (HE grade 1) and severe (HE grades 2-4), according to the degree of impairment of autonomy, and treatment-dependent persistent encephalopathy is a subgroup in whom overt symptoms develop promptly after discontinuing medication.

Minimal HE. The Working Party recognizes the widespread use of the term "subclinical encephalopathy," but wishes to indicate potential misleading consequences of the word "subclinical." For example, subclinical could imply a separate pathogenesis. Others may attribute a lack of clinical importance to this diagnosis. These concepts are discussed in greater detail in subsequent sections.

What Constitutes Minimal Encephalopathy in Patients With Cirrhosis?

Background

In contrast to patients with symptomatic encephalopathy, patients with minimal HE have no recognizable clinical symptoms of brain dysfunction. Therefore, the prerequisite for the diagnosis of minimal HE is the careful exclusion of clinical symptoms.

Diagnosis of Symptomatic HE. The diagnosis of HE is based on a careful neuropsychiatric evaluation. Neurologic findings in patients with cirrhosis and HE are usually confined to the mental and the motor status. Evidence for disordered mentation may be evident when recording the history. Here, emphasis should be

placed on attentiveness to the examiner and evidence for subtle changes in daily living, such as a decrease in energy level; impairment of the sleep-wake cycle; and impairment of cognition, consciousness, or motor function. In the mental-status examination, there must be a careful evaluation of the level of consciousness, attention to and ability to cooperate with the examiner, the speed with which tasks are completed, and affect (does the patient appear apathetic or with a dull affect?). The cranial nerves are usually normal, but hypomimia or dysarthria may be present. Subtle abnormalities may be evident on the motor examination such as an increase in tone, reduced speed or clumsiness of rapid alternating movements, ataxia, an increase in deep tendon reflexes, or impairment of posture or postural reflexes. Observation is needed for abnormal movements such as tremors and particularly asterixis. Primary sensory modalities are usually normal. Evidence for a focal abnormality should suggest an alternate diagnosis. A comprehensive neurologic examination addressing consciousness, orientation, cognitive function, and sensory and motor function together with the knowledge of the patient's history is required to make the diagnosis of HE. Concomitant neurologic disease such as subdural hematoma, Wernicke's disease, intercurrent infection (including encephalitis), other metabolic abnormalities (*e.g.*, water, electrolyte, renal function), and drug intoxications (*e.g.*, alcohol, narcotics, sedatives) must be ruled out.

Diagnosis of Minimal HE. The problem of diagnosing minimal HE is 2-pronged: 1) semantic, and 2) factual.

At the semantic level, a label was originally applied[4] to a population of individuals who performed abnormally on psychometric tests but presented as essentially normal upon clinical neuropsychiatric examination (the depth of the examination is not defined). This observation merely reflects that psychometric tests are more sensitive than observational methods, a finding that has been frequently observed in other neuropsychiatric disorders with dementia. With the advent of sensitive neuroimaging methods and more powerful methods of analyzing brain neuroelectric activity, it is apparent that psychometric tests are not unique and may be even less sensitive in identifying impairment in persons who otherwise appear normal upon clinical examination.

At a factual level, this entity could be explained via two possible scenarios. In the first, minimal encephalopathy may be a different diagnostic entity from either episodic or persistent encephalopathy, with a distinct pathogenesis. Alternatively, the neuropsychiatric disorder encompassing both the clinical and subclinical variants can be quantitatively scaled and qualitatively characterized according to a symptom profile at varying levels of severity. In this scenario, the two entities can be hybridized into one syndrome having qualitatively distinctive features according to severity.

In summary, introduction of the term "subclinical" has led to confusion because its definition has depended on the use of measurements beyond the ordinary reach of clinicians, contributing to a mystique that minimal encephalopathy is a specific disorder. Whereas this possibility exists, it has yet to be demonstrated empirically. The alternative challenge is to determine the clinical dimensions, the best measurement procedures, and a scoring algorithm that can validly diagnose HE throughout the entire spectrum of severity.

Table 2. West Haven Criteria for Semiquantative Grading of Mental State

Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade 2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
	Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Consensus Statement

We propose a large study to redefine neuropsychiatric abnormalities in liver disease. The guiding principle of this study is to consider the dimension of HE as a continuous one. As a result of such an evaluation, a multidimensional definition of HE would be obtained. Minimal encephalopathy would represent a portion of this dimension.

As a neuropsychiatric disorder, HE involves cognitive, affective/emotional, behavioral, and bioregulatory domains. Different traits can be defined within each domain. For example, cognition may include evaluation of psychomotor speed, visuopraxis, attention, concentration, abstracting, and a level of consciousness. Biological regulation is of special interest to the whole spectrum of liver disease, because it would include evaluation of functions such as sleep, appetite, and sexuality. A score for each domain would allow the combination of all 4 domains into one index score using a common metric that is the same across domains. Minimal encephalopathy would be defined according to a cutoff score.

A large sample is required to perform the proposed study. It would have to include all levels of severity of liver disease. Language and cultural differences must be taken into account. Such a large sample will afford the opportunity to develop a valid and replicable distribution of normality and cutoff scores for clinical and minimal HE.

What Are the Best Outcome Measures to Report Efficacy in Therapeutic Trials in HE?

Background

All therapeutic trials in patients with HE can be criticized from the perspective of evidence-based medicine.[5] Criticisms include the large spectrum of clinical conditions summarized under this term, the definition of study endpoints, the treatment of control groups, and the methods used to quantify therapeutic effects. Thus, the Working Party discussed ways to improve the design of future treatment trials. Standards were proposed for quantification of the degree of HE.

Episodic Encephalopathy. The simplest grading of HE is based on clinical findings. The West Haven criteria (Table 2) grades HE from I to IV and is widely used[6]; it is based on changes of consciousness, intellectual function, and behavior. The Glasgow coma scale, measuring the response to eye opening, verbal behavior, and motor responsiveness, quantifies neurologic impairment

Table 3. Proposed Study Designs for Therapeutic Trials in Patients With HE

Study Group	Treatment Endpoint	Proposed Assessment of Treatment	Natural History	Problems for Study Design
Episodic HE	Clinical improvement	Clinical grading, EEG, EP	Well documented	Confounding role of precipitating factors
Persistent HE	Clinical improvement	Clinical grading	Well documented	Most cases are of the mild type
Minimal HE	Neuropsychologic/physiologic parameters	Psychometry: MDF (EEG), P300	Unknown	Clinical impact of improvement in tests unknown
After recovery from episodic HE	Recurrence	Clinical status MDF (EEG)	Liver function: a critical variable	Compliance with current meds
Surgical and/or radiological shunts (TIPS)	Prevention of symptoms	Psychometry MDF (EEG) P300	Well documented	In the case of TIPS, narrowing affects results.

Abbreviations: EP, evoked potentials; MDF, mean dominant frequency.

and is less subject to observer variability than the evaluation of consciousness.[7] In studies of overt manifestations of HE, both grading systems are useful.

Persistent Encephalopathy. In 1977, Conn[8] introduced a scoring scale, the PSE index, subsequently used in many clinical trials. It combines mental state with arterial ammonia levels, degree of asterixis, electroencephalographic (EEG) findings, and the result of the number connection test (NCT). Originally, the NCT was developed to test for organic brain damage in alcoholic patients[9] and later adapted to be used to quantify HE.[10] In episodic (acute) encephalopathy, the PSE index has not been determined to be superior to clinical grading. Its shortcomings limit its use for the quantification of HE in clinical studies of chronic encephalopathy: Mental state, EEG, and the NCT are not independent variables; an arbitrary multiplicator is applied for mental state, the NCT and EEG are given arbitrary units, and no age correction is used for NCT.[11] Psychometric tests also require adjustment to demographic and cultural confounding variables.[12] Arterial ammonia levels are more accurate than venous values, but still correlate poorly with symptoms of HE.[13] Scoring of ammonia levels is again arbitrary.

Minimal HE. *Neuropsychologic tests.* A large number of neuropsychologic tests have been used to describe cognitive abnormalities in patients without clinical evidence of HE. Testing across neuropsychologic domains is possibly the optimal approach[14,15] to identify selective abnormalities in areas such as attention and fine motor function. In only selected instances has the influence of age, sex, education, and cultural differences on these tests been systematically evaluated in patients with liver disease.[11] It is critical to administer and score these tests exactly as specified in the test manuals. Nonadherence will lead to discrepancies between groups and errors in diagnosis. However, the need for shorter evaluations has led to the use of 4 tests in most clinical studies: NCT-A, NCT-B, digit-symbol, and block-design test. The block-design and digit-symbol tests are subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).[16] A standardized test battery including the NCT A and B, the line-tracing, the serial-dotting, and the digit-symbol tests (PSE-Syndrome-Test[17,18]) has a high specificity for HE as compared with other metabolic encephalopathies.[18]

Because of limited experience of participants, new diagnostics tools like the Posner test,[19] the Sternberg Paradigm,[20] or computerized psychometric tests[21] were not discussed at the Working Party.

Neurophysiologic tests. Changes in EEG/evoked responses are nonspecific and do not allow a diagnosis of HE. The simplest EEG assessment in HE is to grade the degree of abnormality of the conventional tracing. A more refined assessment can be obtained using computer-assisted techniques of analysis, including the mean dominant EEG frequency and the power of a particular rhythm.[22-25] Among the most sensitive test of evoked potentials is the P300 peak obtained in an auditory oddball paradigm.[26] The major difficulty in the validation of neuropsychologic and/or neurophysiologic testing has been the lack of a precise definition of what constitutes the "gold standard" for minimal HE. In its absence, the sensitivity and specificity of these tests cannot be fully determined.

Other tests. The PSE index has been used for studies of minimal HE. Its usefulness in this setting has not been prospectively validated. Recently, a quality-of-life questionnaire (sickness impact profile) was used to detect the extent and frequency of deficits in daily functioning in patients with cirrhosis without clinically apparent HE.[27] Impairment of both physical and functional functioning was noted in patients with abnormal neuropsychologic and/or neurophysiologic testing. Impaired quality of life is not necessarily related to the presence or absence of HE.[28]

Consensus Statement

Quantification of HE in clinical trials should take into account the multiaxial definition of HE proposed in the first statement as well as the clinical endpoint. This is a continuously evolving field, and investigators should be aware of the need for prospective validation studies.

For Episodic or Persistent Encephalopathy. Clinical grading of the abnormal mental state should be used for quantification. Stages I-IV include changes in consciousness, intellectual function, and behavior. The Glasgow coma scale is useful for patients in stages III and IV.

For Minimal Encephalopathy. *Neuropsychologic tests.* At least two of the following should be used: NCT-A, NCT-B, block-design test, digit-symbol test. A standardized test battery including the NCT A and B, the line-tracing test, the serial-dotting test, and the digit-symbol test (PSE-Syndrome-Test[18]) is recommended.

Neurophysiologic tests. When possible, quantitative neurophysiologic tools (like EEG with mean dominant frequency, P300 auditory evoked potentials) should be used.

For Clinical End Point. The optimal study design depends on what type of patients are addressed. Table 3 summarizes the various possibilities. Investigators and regulatory agencies should be aware that there is no established "gold-standard" treatment of any kind of HE, and thus all future trials should strive to include a placebo or a standard treatment arm (which should not include drugs like lactulose or neomycin).

Prevention of HE. Two clinical situations now arise in which prevention of new or recurrent episodes of encephalopathy is the goal. This includes patients who have recovered from an episode of HE or patients in whom *de novo* HE should be prevented after placement of a transjugular intrahepatic portal-systemic shunt (TIPS) stent. The efficacy of such a treatment can be assessed on clinical grounds alone (*i.e.*, the number of episodes in two study groups) or using neurophysiologic or psychometric tests.

What Is The Role Of Current Neuroimaging Techniques For The Diagnosis Of HE?

Background. In the past decade and a half, there has been a major revolution in neuroimaging. Modalities such as magnetic resonance imaging and spectroscopy, computed x-ray tomography, and positron emission tomography (PET) allow the rapid and noninvasive evaluation of structural, physiologic, and biochemical features of the brain. Thus, neuroimaging might make a significant contribution to the evaluation and management of patients with HE.

Computed X-ray Tomography. This imaging modality plays an important role in the evaluation of acute neurologic symptoms. Information in patients with cirrhosis without encephalopathy is more controversial. In one study, anatomic abnormalities, attributed to atrophy and edema, correlated with neuropsychologic test performance.[29] The role of brain atrophy in the development of symptoms has not been fully elucidated.[30]

Magnetic Resonance Imaging. Patients with cirrhosis, even without clinical evidence of HE, exhibit symmetrical high-signal abnormalities in the pallidum on T_1-weighted images.[31,32] Deeper inspection of the T_1 signal indicates a generalized increase in white matter, limbic, and other extrapyramidal structures.[33] These abnormalities become more prominent as liver function declines and may regress after liver transplantation.[34] An accumulation of manganese may explain the T_1 abnormality.[35,36]

Magnetic Resonance Spectroscopy. This technique, with appropriate attention to quality control and standardization, can produce measures of common chemicals in the brain. Field strengths of 1.5 T have been commonly used. ^{1}H-Spectra have shown a characteristic pattern: an increase in the glutamine/glutamate peak coupled with a decrease in the myo-inositol and choline signal.[37,38] This is thought to represent disturbances in cell-volume homeostasis. In contrast to proton spectroscopic studies, there is little agreement among ^{31}P studies. While some studies have shown altered concentrations of phosphocreatine, inorganic phosphate, and adenosine triphosphate, others fail to confirm these observations.[39] The reasons for these discrepancies are unclear.

Positron Emission Tomography. This technique can provide images of the brain that reflect a specific biochemical or physiologic process. The exact nature of the image depends on the tracer used. PET measurements of cerebral blood flow (^{15}O-water) and ammonia metabolism (^{13}N) in patients with cirrhosis have demonstrated a rise in the cerebral ammonia metabolic rate coupled with an increase in the permeability surface area of the blood brain barrier to ammonia.[40] Glucose metabolism can be examined with ^{18}F-fluorodeoxyglucose. A study has shown reduced metabolism in the anterior cingulate, a region whose impairment may affect attentional systems in the brain.[41] PET is expensive, time consuming, and the measurements are difficult to interpret.

Consensus Statement. HE is a clinical condition characterized by the presence of cerebral dysfunction in patients with liver disease. It is not identified by structural abnormalities that are visible at the gross anatomic level, making neuroimaging techniques more important to rule out other lesions than to arrive at a positive diagnosis. Imaging techniques based on biochemical changes may be eventually useful in the diagnosis of HE. Newer technical developments, including magnetic resonance spectroscopy machines with a higher field strength and the use of labeled neurotransmitters and/or neurotransmitter analogs with PET scanning, offer special promise. However, these newer approaches must be subjected to the combined tests of sensitivity, specificity, and cost-effectiveness, an approach mostly absent on most of the evaluations of current neuroimaging methods. In spite of their immense potential in research, the current expense of these studies limits their clinical applicability.

In Summary

In summary, the Working Party has suggested:

- A modification of current nomenclature for clinical diagnosis of HE.
- Guidelines for the performance of clinical trials in HE including the use of the PHES test. A temporary consensus on PHES is proposed as a means to standardize the diagnosis of minimal encephalopathy.
- A large study to redefine neuropsychiatric abnormalities in liver disease that would allow the diagnosis of minimal encephalopathy on firm statistical grounds.
- The need for a careful evaluation of the newer neuroimaging modalities for the diagnosis of HE.

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