Hepatic encephalopathy in adults: Clinical manifestations and diagnosis

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INTRODUCTION

Hepatic encephalopathy describes a spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction and/or portosystemic shunting. Overt hepatic encephalopathy develops in 30 to 45 percent of patients with cirrhosis and in 10 to 50 percent of patients with transjugular intrahepatic portal-systemic shunts [1,2]. The International Society for Hepatic Encephalopathy and Nitrogen Metabolism consensus defines the onset of disorientation or asterixis as the onset of overt hepatic encephalopathy [3]. Some patients with hepatic encephalopathy have subtle findings that may only be detected using specialized tests, a condition known as minimal hepatic encephalopathy [4-6]. Minimal hepatic encephalopathy is seen in up to 80 percent of patients with cirrhosis [7-13].

Hepatic encephalopathy is often easy to detect in patients presenting with overt neuropsychiatric symptoms. It may be more difficult to detect in patients with chronic liver diseases who have mild signs of altered brain function, particularly if the underlying cause of the liver disease may be associated with neurologic manifestations (such as alcohol-associated liver disease or Wilson disease).

This topic will review the clinical manifestations and diagnosis of hepatic encephalopathy in adults. The pathogenesis and treatment of hepatic encephalopathy are discussed elsewhere. (See "Hepatic encephalopathy: Pathogenesis" and "Hepatic encephalopathy in adults: Treatment".)

CATEGORIZATION AND GRADING

Hepatic encephalopathy is categorized based on several factors: the severity of manifestations, the time course, and whether precipitating factors are present [14].

- **Severity of manifestations** – The severity of hepatic encephalopathy is graded based on the clinical manifestations (table 1 and figure 1) [14] (see 'Clinical manifestations' below):

  - Minimal: Abnormal results on psychometric or neurophysiological testing without clinical manifestations (see 'Psychometric tests' below)
  - Grade I: Changes in behavior, mild confusion, slurred speech, disordered sleep
  - Grade II: Lethargy, moderate confusion
  - Grade III: Marked confusion (stupor), incoherent speech, sleeping but arousable
  - Grade IV: Coma, unresponsive to pain

  Patients with grade I encephalopathy may have mild asterixis, whereas pronounced asterixis is seen in patients with grade II or III encephalopathy [15]. Asterixis is typically absent in patients with grade IV encephalopathy, who instead may demonstrate decorticate or decerebrate posturing.

  Patients with minimal or grade I hepatic encephalopathy are described as having covert hepatic encephalopathy, whereas patients with grade II to IV hepatic encephalopathy are described as having overt hepatic encephalopathy. The separation of minimal hepatic encephalopathy from grade I hepatic encephalopathy is important for clinical studies.

- **Time course** – The time course for hepatic encephalopathy can be episodic, recurrent (bouts of hepatic encephalopathy that occur within a time interval of six months or less), or persistent (a pattern of behavioral alterations that are always present, interspersed with episodes of overt hepatic encephalopathy).

- **Precipitating factors** – Episodes of hepatic encephalopathy are described as being either nonprecipitated or precipitated. If precipitated, the precipitating factors should be specified (table 2). (See 'Evaluation for precipitating causes' below.)

CLINICAL MANIFESTATIONS

Hepatic encephalopathy is characterized by cognitive deficits and impaired neuromuscular function (figure 1 and figure 2). Patients with minimal hepatic encephalopathy have subtle

cognitive deficits, often appear to be asymptomatic, and may only be detected with psychomotor or electrophysiologic testing. Patients with overt hepatic encephalopathy have signs and symptoms that can be detected clinically, without the use of psychomotor testing (though psychomotor testing may be helpful in evaluating patients with mild encephalopathy).

In addition to the clinical manifestations of hepatic encephalopathy, patients frequently have clinical manifestations of chronic liver disease.

Signs and symptoms — Cognitive findings in patients with hepatic encephalopathy vary from subtle deficits that are not apparent without specialized testing (minimal hepatic encephalopathy), to more overt findings, with impairments in attention, reaction time, and working memory (figure 1 and figure 2) [16]. Patients with severe hepatic encephalopathy may progress to hepatic coma.

Disturbances in the diurnal sleep pattern (insomnia and hypersomnia) are common initial manifestations of hepatic encephalopathy and typically precede other mental status changes or neuromuscular symptoms. As hepatic encephalopathy progresses, patients may develop mood changes (euphoria or depression), disorientation, inappropriate behavior, somnolence, confusion, and unconsciousness.

Neuromuscular impairment in patients with overt hepatic encephalopathy includes bradykinesia, asterixis (flapping motions of outstretched, dorsiflexed hands), slurred speech, ataxia, hyperactive deep tendon reflexes, and nystagmus. Less commonly, patients develop loss of reflexes, transient decerebrate posturing, and coma.

Focal neurologic deficits may also be present. In a report of 32 patients who had 46 episodes of hepatic encephalopathy, a focal neurologic sign was detected in eight patients (17 percent of the episodes) [17]. The most common was hemiplegia. None of the patients with focal neurologic signs had abnormal findings on computed tomography scan or cerebrospinal fluid examination. Cerebral magnetic resonance imaging was performed in five of the eight patients and was normal in all five. Similarly, five patients with focal neurologic signs underwent Doppler ultrasound of the neck and vessels. In all five, the Doppler imaging was normal. The focal neurologic deficits resolved completely in seven of eight surviving patients after six months of follow-up.

Patients with hepatic encephalopathy usually have advanced chronic liver disease (decompensated cirrhosis) and thus have many of the physical stigmata associated with severe hepatic dysfunction. Physical findings may include muscle wasting, jaundice, ascites, palmar erythema, edema, spider telangiectasias, and fetor hepaticus. Some of these findings (such as muscle wasting, spider telangiectasias, and palmar erythema) are usually absent in previously

healthy patients with acute hepatic failure since their development requires a relatively longer period of hepatic dysfunction. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations' and "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

Sarcopenia is a syndrome of decreased muscle mass, strength, and function that has been identified as a risk factor for hepatic encephalopathy, and this is possibly related to impaired detoxification of ammonia [18]. In a meta-analysis of five studies including 1713 patients with cirrhosis, sarcopenia was associated with higher risk of mild and overt hepatic encephalopathy compared with no sarcopenia (pooled odds ratio [OR] 3.34, 95% CI 1.68-6.67 and OR 2.05, 95% CI 1.28-3.29, respectively) [19].

Laboratory abnormalities — Laboratory abnormalities in patients with hepatic encephalopathy may include elevated arterial and venous ammonia concentrations. In addition, patients typically have abnormal liver biochemical and synthetic function tests due to underlying liver disease. Patients may also have electrolyte disturbances (such as hyponatremia and hypokalemia) related to hepatic dysfunction and/or diuretic use. (See 'Ammonia' below and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Laboratory findings'.)

DIAGNOSIS

The approach to the diagnosis of hepatic encephalopathy includes:

- A history and physical examination to detect the cognitive and neuromuscular impairments that characterize hepatic encephalopathy.
- Exclusion of other causes of mental status changes (see 'Differential diagnosis' below).
  - Serum laboratory testing to rule out metabolic abnormalities.
  - A computed tomography (CT) scan of the brain if the clinical findings suggest another cause for the patient's findings may be present (such as a subdural hematoma from trauma); a CT scan may also demonstrate cerebral edema (found in 80 percent of patients with acute hepatic encephalopathy) (see "Acute toxic-metabolic encephalopathy in adults", section on 'Hepatic encephalopathy').
- Evaluation for possible precipitating causes of the hepatic encephalopathy (see 'Evaluation for precipitating causes' below).

While arterial and venous ammonia concentrations are often elevated in patients with hepatic encephalopathy, an elevated ammonia level is not required to make the diagnosis. In addition, elevated ammonia levels may be seen in patients who do not have hepatic encephalopathy (table 3).

For patients with mild degrees of hepatic encephalopathy (minimal hepatic encephalopathy or grade I encephalopathy) in whom the diagnosis is unclear, psychometric and electrophysiologic tests may be helpful. In such patients, our approach is to first to ask about subtle signs of impaired mental status, and if signs point to the possible presence of minimal hepatic encephalopathy to perform psychometric testing (typically the number connection test) (algorithm 1). An alternative but less sensitive test is the Mini-Mental State Examination (MMSE). (See "The mental status examination in adults", section on 'Cognitive screening tests'.)

For patients with more severe hepatic encephalopathy (grades III and IV), the Glasgow Coma Scale may be useful for further stratifying the severity of neurologic impairment (figure 1) [20]. (See 'Psychometric tests' below and 'Electrophysiologic tests' below and 'Clinical manifestations' above.)

History and physical examination — The evaluation should start by inquiring about mental status changes, keeping in mind that in patients with minimal hepatic encephalopathy the signs may be subtle. Patients should be asked about changes in their sleep patterns and in cognitive capacity (decreased attention span, impaired short term memory) leading to difficulties with normal daily activities. Patients should also be asked about impaired work performance and work- or driving-related accidents. Patients should also be examined for signs of neuromuscular dysfunction. (See 'Clinical manifestations' above.)

Laboratory tests — Ammonia is the best characterized neurotoxin that precipitates hepatic encephalopathy. However, an elevated serum ammonia concentration is not required to make the diagnosis and is not specific for hepatic encephalopathy. In addition, ammonia levels are influenced by factors such as how the blood sample is obtained and handled. Serum ammonia levels should **not** be used to screen for hepatic encephalopathy in patients who are asymptomatic or who have mental status changes in the absence of liver disease or a portal-systemic shunt.

Other routine laboratory tests should be obtained to exclude other causes of mental status changes (eg, hypoglycemia, uremia, electrolyte disturbances, and intoxication) and to look for conditions that may have precipitated the hepatic encephalopathy. (See 'Differential diagnosis' below and 'Evaluation for precipitating causes' below.)

Ammonia — The gastrointestinal tract is the primary source of ammonia, which enters the circulation via the portal vein. Ammonia is produced by enterocytes from glutamine and by colonic bacterial catabolism of nitrogenous sources, such as ingested protein and secreted urea. The intact liver clears almost all of the portal vein ammonia, converting it into urea or glutamine and preventing entry into the systemic circulation. The increase in blood ammonia levels in advanced liver disease is a consequence of impaired liver function and of shunting of blood around the liver. Muscle wasting may contribute since muscle is an important site for extrahepatic ammonia removal.

Whether to measure the serum ammonia concentration in patients suspected of having hepatic encephalopathy remains controversial. While the venous and arterial ammonia levels correlate with the severity of hepatic encephalopathy, levels are inconsistently elevated [21,22]. Measuring serum ammonia levels is not required to make the diagnosis of hepatic encephalopathy or for the long-term follow-up of patients with advanced chronic liver disease. Furthermore, ammonia levels can be elevated in a variety of nonhepatic conditions (table 3).

Neither arterial or venous ammonia concentration is useful in screening for hepatic encephalopathy [23].

Other potential markers — Serum levels of 3-nitrotyrosine may be elevated in patients with minimal hepatic encephalopathy. One study found that using a cutoff of 14 nM, 3-nitrotyrosine was 93 percent sensitive and 89 percent specific for detecting minimal hepatic encephalopathy [24].

Psychometric tests — Commonly performed bedside tests are insufficiently sensitive to detect subtle changes in mental function. As a result, several psychometric tests have been evaluated that quantify the impairment of mental function in patients with mild stages of hepatic encephalopathy [4,25-28]. These tests are more sensitive for the detection of minor deficits of mental function than conventional clinical assessment or an EEG [25]. Several psychometric tests have been developed, but none is used routinely in clinical practice. Our approach is to use the number connection test if signs point to the possible presence of minimal hepatic encephalopathy.

The use of psychometric tests is limited because many are cumbersome and time consuming (up to two hours per session), their reliability is decreased by a learning effect when they are applied repeatedly, and there is poor correlation among the tests [29,30]. Another issue with psychometric tests is that they are nonspecific (ie, they cannot differentiate among multiple underlying conditions that may lead to similar test results) [31]. This is a particular problem in

patients with alcohol-associated liver disease or Wilson disease since both are associated with central nervous system abnormalities.

Number connection test (Reitan Test) — The most frequently used psychometric test is the number connection test (NCT or Reitan Test), which is easily administered and interpreted (figure 3 and figure 4) [26,27,32]. The NCT is a timed connect-the-numbers test. Patients without hepatic encephalopathy should finish the test in a number of seconds less than or equal to their age in years. In other words, if a patient is 50 years old, he should be able to finish the test in ≤50 seconds.

The test traditionally has two parts, but often only the first part of the test (figure 3) is used because the second part (figure 4) can be confusing and often does not add additional clinical information.

Other psychometric tests

Electrophysiologic tests — Electrophysiologic tests to detect minimal hepatic encephalopathy include EEG monitoring, evoked potentials, and critical flicker frequency testing [33-36]. However, none of these tests is widely used.

Electroencephalogram (EEG) activity — The evolving EEG changes associated with increasingly severe hepatic encephalopathy consist initially of a bilaterally synchronous decrease in wave frequency and an increase in wave amplitude, associated with the disappearance of a readily discernible normal alpha-rhythm (8 to 13 cps). The simplest EEG assessment of hepatic encephalopathy is grading the degree of abnormality of the conventional EEG tracing. A more refined assessment can be accomplished with computer-assisted spectral analysis of the EEG, which permits variables in the EEG (such as the mean dominant EEG frequency and the power of a particular EEG rhythm) to be quantified. Minor changes in the dominant EEG frequency occur in mild hepatic encephalopathy. Spectral EEG analysis may improve the assessment of mild hepatic encephalopathy by decreasing inter-operator variability and providing reliable parameters correlated with mental status [33].

The bispectral index (BIS) monitor is a rapid bedside tool to monitor EEG activity. In a prospective study, BIS monitoring was useful for grading and monitoring the degree of involvement of the central nervous system in patients with chronic liver disease and to classify the degree and progression of hepatic encephalopathy [34].

Radiologic imaging — Radiologic imaging is primarily used to exclude other causes of mental status changes. We typically obtain a noncontrast head CT scan when the clinical findings

suggest that another cause for the patient's mental status changes may be present (such as a subdural hematoma from trauma).

Computed tomography and magnetic resonance imaging of the brain — A noncontrast CT scan is indicated in patients with overt hepatic encephalopathy in whom the diagnosis is uncertain, to exclude other diseases associated with coma or confusion. A CT scan may also reveal generalized or localized cerebral edema, suggesting a diagnosis of hepatic encephalopathy.

Magnetic resonance imaging — Magnetic resonance imaging (MRI) is superior to CT for the diagnosis of brain edema in liver failure, but it is not an established method for diagnosing hepatic encephalopathy. Changes have been observed on T1-weighted images with a strong signal in the basal ganglia in patients with hepatic encephalopathy, possibly due to manganese accumulation [37]. However, these changes are neither sensitive nor specific indicators of hepatic encephalopathy [38,39].

Evaluation for precipitating causes — There are several conditions that may precipitate an episode of hepatic encephalopathy in patients with liver disease or a portal-systemic shunt (table 2). These include [16,40-43]:

- Gastrointestinal bleeding
- Infection (including spontaneous bacterial peritonitis and urinary tract infections)
- Hypokalemia and/or metabolic alkalosis
- Renal failure
- Hypovolemia
- Hypoxia
- Sedative or benzodiazepine use
- Hypoglycemia
- Constipation
- Rarely, hepatocellular carcinoma and/or vascular occlusion (hepatic vein or portal vein thrombosis)

Patients with hepatic encephalopathy should be evaluated for potential precipitating causes. This evaluation should include:

- A history to determine if the patient has been exposed to any medications or toxins (including alcohol)
- Physical examination to look for signs of gastrointestinal bleeding or hypovolemia (see "Approach to acute upper gastrointestinal bleeding in adults", section on 'Bleeding

manifestations' and "Etiology, clinical manifestations, and diagnosis of volume depletion in adults", section on 'Clinical manifestations')

- A search for sources of infection with blood and urine cultures, as well as paracentesis for patients with ascites (see "Spontaneous bacterial peritonitis in adults: Diagnosis")
- Routine serum chemistries to look for metabolic and electrolyte abnormalities
- Serum alpha-fetoprotein (see "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Alpha-fetoprotein')

●Urine drug screen. Some patients covertly use medications (eg, sedatives) that may precipitate hepatic encephalopathy requiring hospital admission.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients presenting with mental status changes is long (table 4). While hepatic encephalopathy should be considered in patients with acute or chronic liver disease or a portal-systemic shunt, particularly those with a history of hepatic encephalopathy, other causes for the patient's confusion should be considered, such as a subdural hematoma, renal failure, or mental status changes associated with the patient's underlying liver disease (eg, Wilson disease).

A general approach to the evaluation of patients with delirium and confusional status is discussed elsewhere. (See "Diagnosis of delirium and confusional states".)

CAPACITY TO DRIVE

We advise patients to avoid driving following an episode of overt hepatic encephalopathy. For patients who want to resume driving, we advise them to contact their local department of motor vehicles for a driving assessment based on local regulations. We agree with guidance from professional societies that assessing the ability to drive should be done according to local regulations because psychometric tests cannot reliably determine if the patient is a safe driver [44].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cirrhosis" and "Society guideline links: Adult with altered mental status in the emergency department".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hepatic encephalopathy (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definition** – Hepatic encephalopathy describes the spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction. (See 'Introduction' above.)

- **Clinical manifestations** – Hepatic encephalopathy is characterized by cognitive deficits and impaired neuromuscular function (figure 1 and figure 2). Cognitive findings in patients with hepatic encephalopathy vary from subtle deficits that are not apparent without specialized testing (minimal hepatic encephalopathy) to more overt findings, with impairments in attention, reaction time, and working memory. Patients with severe hepatic encephalopathy may progress to hepatic coma. Neuromuscular impairments include bradykinesia, hyperreflexia, rigidity, myoclonus, and asterixis. Disturbances in the diurnal sleep pattern (insomnia and hypersomnia) are common initial manifestations of hepatic encephalopathy and typically precede other mental status changes or neuromuscular symptoms. (See 'Clinical manifestations' above and 'Categorization and grading' above.)

- **Diagnosis** – The approach to the diagnosis of hepatic encephalopathy includes (algorithm 1) (see 'Diagnosis' above):

  - A history and physical examination to detect the cognitive and neuromuscular impairments that characterize hepatic encephalopathy.

  - Psychometric testing if minimal hepatic encephalopathy is suspected.
  - Exclusion of other causes of mental status changes: Serum laboratory testing to rule out metabolic abnormalities, a computed tomography scan of the brain if the clinical findings suggest another cause for the patient's findings may be present (such as a subdural hematoma from trauma).

  While arterial and venous ammonia concentrations are often elevated in patients with hepatic encephalopathy, an elevated ammonia level is not required to make the diagnosis. In addition, elevated ammonia levels may be seen in patients who do not have hepatic encephalopathy (table 3).

- **Evaluation for precipitating causes** – Patients with hepatic encephalopathy should be evaluated for potential precipitating causes (table 2). This evaluation should include (see 'Evaluation for precipitating causes' above):

  - A history to determine if the patients have been exposed to any medications or toxins (including alcohol)
  - Physical examination to look for signs of gastrointestinal bleeding or hypovolemia
  - A search for sources of infection with blood and urine cultures, as well as paracentesis for patients with ascites
  - Routine serum chemistries to look for metabolic and electrolyte abnormalities
  - Serum alpha-fetoprotein
  - Urine drug screen

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GRAPHICS

West Haven criteria for hepatic encephalopathy

WHC including MHE	ISHEN	Description	Suggested operative criteria	Comment
Unimpaired		▪ No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	▪ Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I		▪ Trivial lack of awareness ▪ Euphoria or anxiety ▪ Shortened attention span ▪ Impairment of addition or subtraction ▪ Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	▪ Lethargy or apathy ▪ Disorientation for time ▪ Obvious personality change ▪ Inappropriate behavior ▪ Dyspraxia ▪ Asterixis	Disoriented for time (at least three of the following are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent

Grade III		▪ Somnolence to semistupor ▪ Responsive to stimuli ▪ Confused ▪ Gross disorientation ▪ Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		▪ Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or portosystemic shunting.

WHC: West Haven criteria; MHE: minimal hepatic encephalopathy; ISHEN: International Society for Hepatic Encephalopathy and Nitrogen Metabolism; HE: hepatic encephalopathy.

Graphic 101898 Version 1.0

Clinical features of hepatic encephalopathy in adults

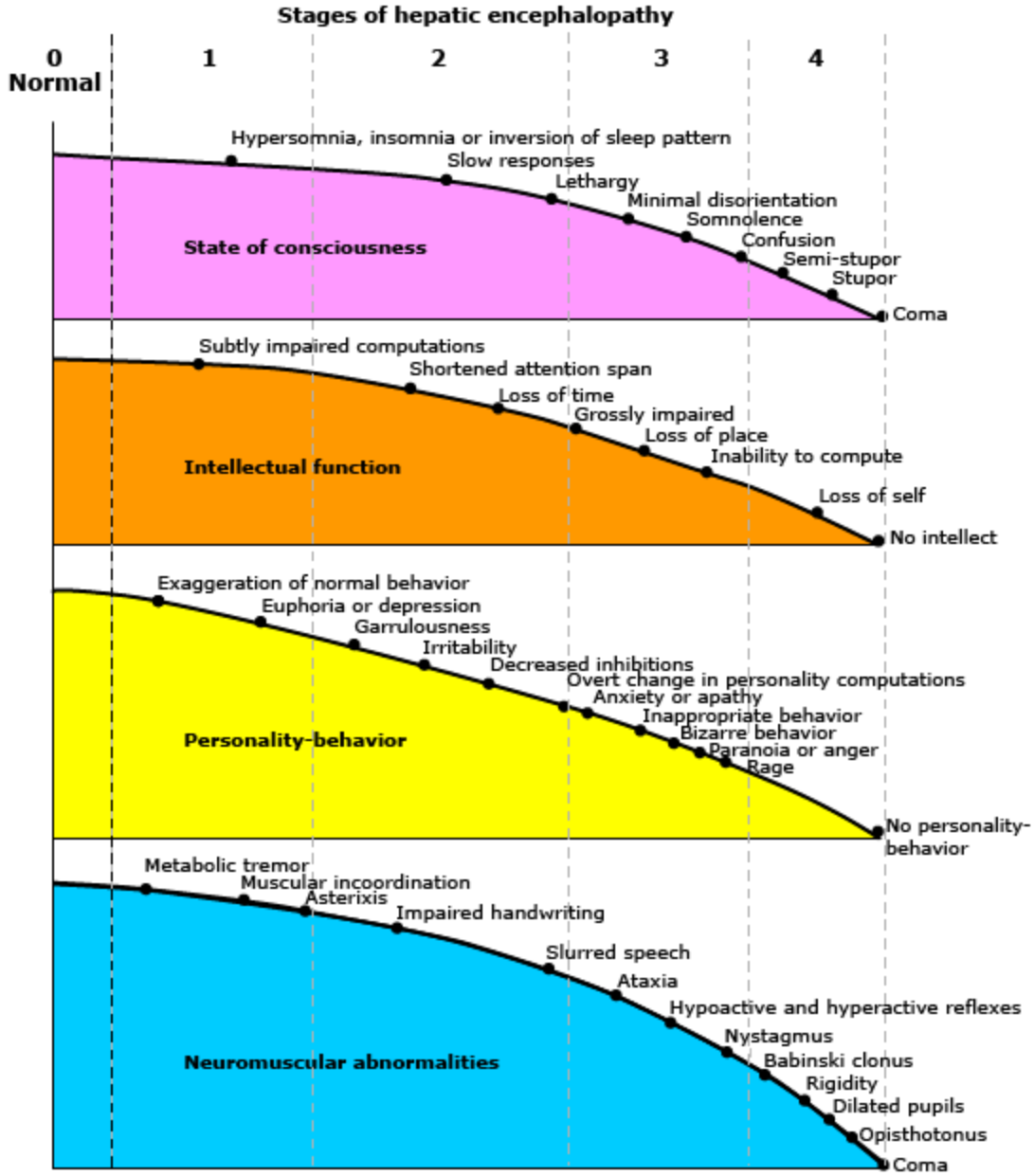


Diagram depicting the grade of hepatic encephalopathy in adults and the clinical features associated with advancing stages.

Data from: Conn HO, Lieberthal MM. The hepatic coma syndromes and lactulose. Lippincott Williams & Wilkins, Baltimore 1979.

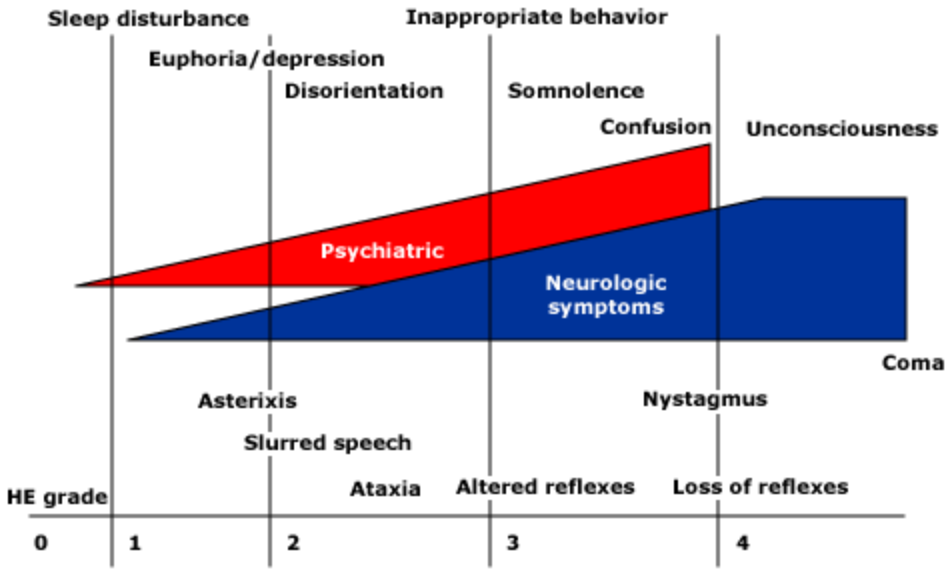
Graphic 70740 Version 6.0

Precipitants of hepatic encephalopathy in patients with cirrhosis

Drugs
Benzodiazepines
Nonbenzodiazepine hypnotics (eg, zolpidem)
Narcotics
Alcohol
Increased ammonia production, absorption or entry into the brain
Excess dietary intake of protein
Gastrointestinal bleeding
Infection
Electrolyte disturbances such as hypokalemia
Constipation
Metabolic alkalosis
Dehydration
Vomiting
Diarrhea
Hemorrhage
Diuretics
Large volume paracentesis
Portosystemic shunting
Radiographic or surgically placed shunts
Spontaneous shunts
Vascular occlusion
Hepatic vein thrombosis
Portal vein thrombosis
Primary hepatocellular carcinoma

Graphic 50440 Version 4.0

Evolution of hepatic encephalopathy



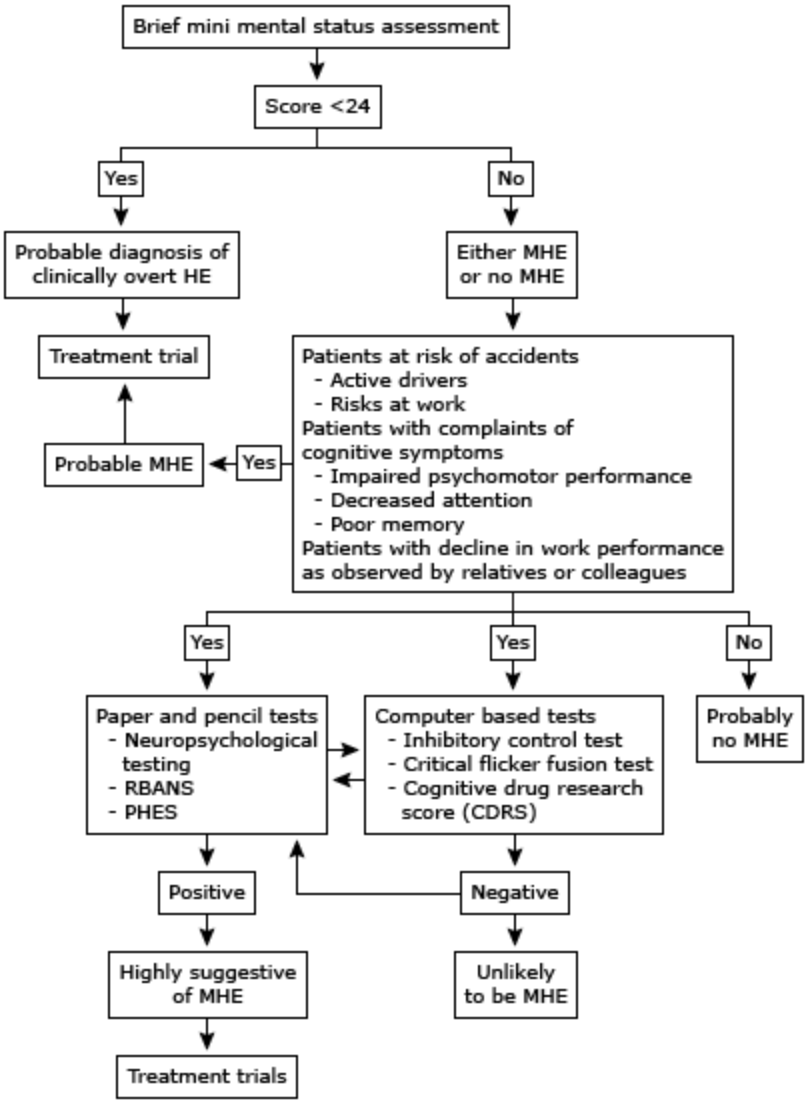
Graphic 58163 Version 1.0

Differential diagnosis of hyperammonemia

Reye syndrome
Gastrointestinal bleeding
Renal disease
Urinary tract infection with a urease-producing organism (eg, *Proteus mirabilis*)
Ureterosigmoidostomy
Shock
Severe muscle exertion/heavy exercise
Cigarette smoking
Transient hyperammonemia in newborns
Certain inborn errors of metabolism (urea cycle defects and organic acidemia)
Any cause of portosystemic shunting of blood
Parenteral nutrition
After high-dose chemotherapy
Drugs such as:
Valproic acid
Barbiturates
Narcotics
Diuretics
Alcohol
Salicylate intoxication
Systemic *Mycoplasma hominis* or *Ureasplasma* spp infection in lung transplant recipients

Graphic 57620 Version 3.0

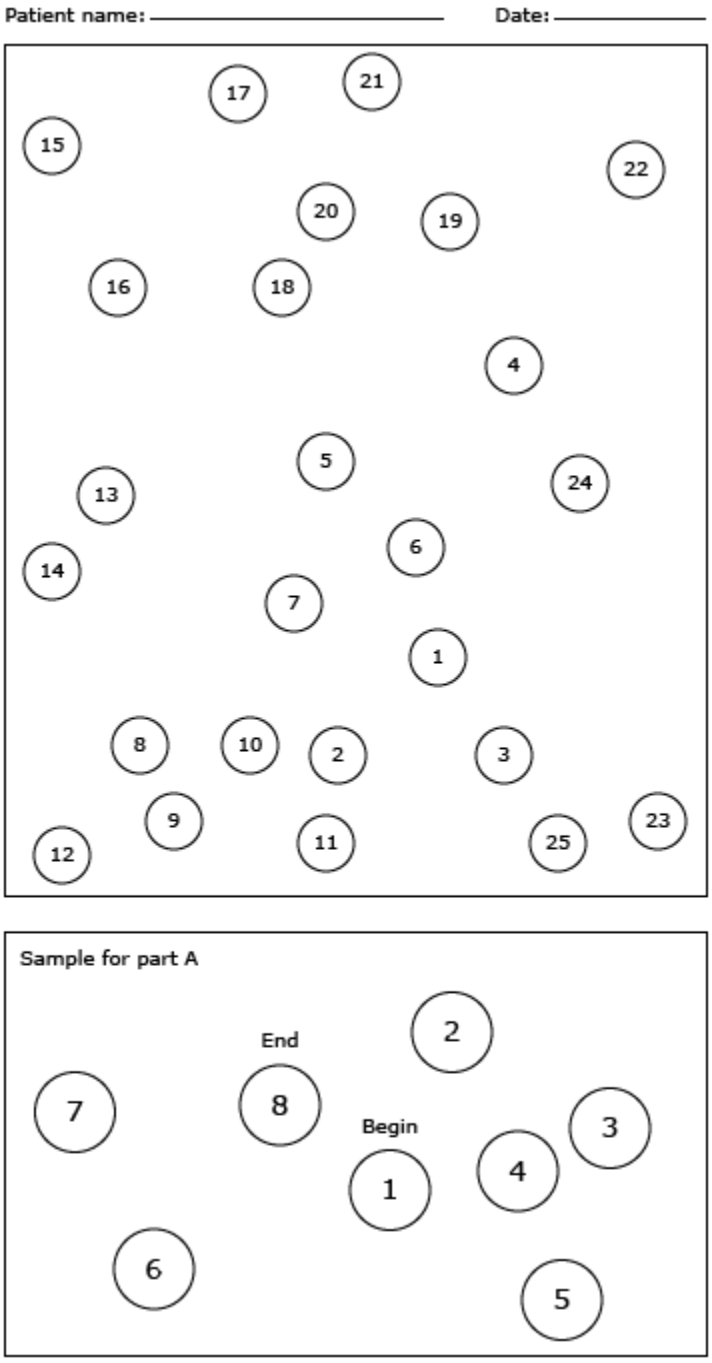
Testing and treatment for minimal hepatic encephalopathy



HE: hepatic encephalopathy; MHE: minimal hepatic encephalopathy; PHES: psychometric hepatic encephalopathy score; RBANS: repeatable battery for the assessment of neuropsychological status.

Graphic 90152 Version 1.0

Reitan Test for hepatic encephalopathy (part A)



The Reitan Test (number connection test) is a commonly used bedside test that is useful for screening for hepatic encephalopathy.

- Step 1: Make sure that the patient is alert enough to cooperate for this test, can see adequately, has a writing surface, is able to count, and can hold a pen or pencil.
- Step 2: Demonstrate to the patient how to connect the numbers on the sample for part A (lower box).
- Step 3: Inform the patient that you will be timing the test and to complete the number connections from 1 to 25 as fast as

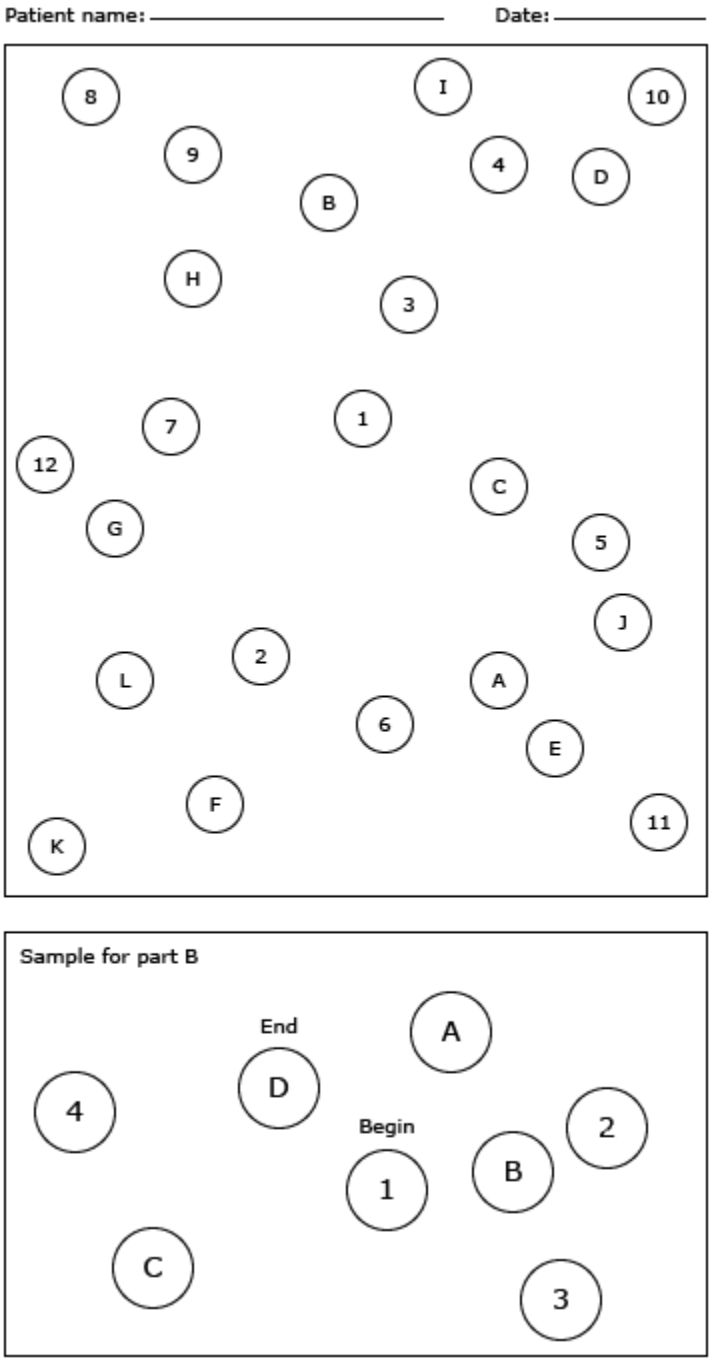
the patient can without lifting the pen or pencil from the paper.

- Step 4: If an error occurs, point it out immediately and allow the patient to correct the error. The total elapsed time to complete the test, including the time spent correcting errors, is the score.
- Step 5: Record the time spent to complete the test. If it takes longer than 3 minutes to complete test A, record ">3 minutes" as the score.

An alert person without hepatic encephalopathy should be able to complete part A of the test in seconds similar to their age in years.

Graphic 83108 Version 5.0

Reitan Test for hepatic encephalopathy (part B)



The Reitan Test (number connection test) is a commonly used bedside test that is useful for screening for hepatic encephalopathy. Part B of the test may follow completion of part A, but is not used by all clinicians.

- Step 1: Make sure that the patient is alert enough to cooperate for this test, can see adequately, has a writing surface, is able to count, and can hold a pen or pencil.
- Step 2: Demonstrate to the patient how to connect the numbers and letters on the sample for part B (lower box),

alternating between the numbers and letters (ie, 1-A-2-B-3-C, etc).

- Step 3: Inform the patient that you will be timing the test and to complete the number-letter connections from 1 to L as fast as the patient can without lifting the pen or pencil from the paper.
- Step 4: If an error occurs, point it out immediately and allow the patient to correct the error. The total elapsed time to complete the test, including the time spent correcting errors, is the score.
- Step 5: Record the time spent to complete the test. An average score is 75 seconds, while >273 seconds is considered deficient.

Graphic 83109 Version 3.0

Common causes of delirium and confusional states

Drugs and toxins
Prescription medications (eg, opioids, sedative-hypnotics, antipsychotics, lithium, skeletal muscle relaxers, polypharmacy)
Nonprescription medications (eg, antihistamines)
Drugs of abuse (eg, ethanol, heroin, hallucinogens, nonmedicinal use of prescription medications)
Withdrawal states (eg, ethanol, benzodiazepines)
Medication side effects (eg, hyperammonemia from valproic acid, confusion from quinolones, serotonin syndrome)
Poisons:
Atypical alcohols (ethylene glycol, methanol)
Inhaled toxins (carbon monoxide, cyanide, hydrogen sulfide)
Plant-derived (eg, Jimson weed, Salvia)
Infections
Sepsis
Systemic infections; fever-related delirium
Metabolic derangements
Electrolyte disturbance (elevated or depressed): sodium, calcium, magnesium, phosphate
Endocrine disturbance (depressed or increased): thyroid, parathyroid, pancreas, pituitary, adrenal
Hypercarbia
Hyperglycemia and hypoglycemia
Hyperosmolar and hypoosmolar states
Hypoxemia
Inborn errors of metabolism: porphyria, Wilson disease, etc
Nutritional: Wernicke encephalopathy, vitamin B12 deficiency, possibly folate and niacin deficiencies
Brain disorders
CNS infections: encephalitis, meningitis, brain or epidural abscess
Epileptic seizures, especially nonconvulsive status epilepticus*
Head injury*
Hypertensive encephalopathy

Psychiatric disorders*
Systemic organ failure
Cardiac failure
Hematologic: thrombocytosis, hypereosinophilia, leukemic blast cell crisis, polycythemia
Liver failure: acute, chronic
Pulmonary disease, including hypercarbia and hypoxemia
Renal failure: acute, chronic
Physical disorders
Burns
Electrocution
Hyperthermia
Hypothermia
Trauma: with systemic inflammatory response syndrome, head injury*, fat embolism

CNS: central nervous system.

* Disorders that, while not truly systemic or "medical," may produce the clinical picture of delirium or confusional state in all other aspects.

Graphic 59893 Version 5.0

Contributor Disclosures

Bruce A Runyon, MD, FAASLD No relevant financial relationship(s) with ineligible companies to disclose. **Bruce A Runyon, MD, FAASLD** No relevant financial relationship(s) with ineligible companies to disclose. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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