Hepatic encephalopathy (HE) is a heterogeneous disease that develops as a result of serious liver disease, such as in fulminant hepatitis or cirrhosis, or a portosystemic shunt. It manifests as a spectrum of abnormalities involving cognition, attention, functional ability, personality and intellect. The neuropsychiatric impairment associated with HE can range from mild alteration of cognition and consciousness to coma, depending on the stage of the illness.

The working party proposed a nomenclature that defines HE with respect to the nature of the hepatic abnormality and the duration and characteristics of neurological manifestations. The nomenclature broadly categorizes HE according to the nature of the hepatic abnormality into three types, as follows:

- **Type A.** HE associated with acute liver failure.
- **Type B.** HE associated with portosystemic bypass and no intrinsic hepatocellular disease.
- **Type C.** HE associated with cirrhosis and portal hypertension or portosystemic shunts.
Type A HE is characterized by astrocyte swelling leading to cytotoxic edema and its complications (intracranial hypertension, brain herniation), whereas types B and C are characterized by so-called Alzheimer type II changes in the astrocytes. Such changes include nuclear cell swelling, margination of the chromatin pattern and glycogen accumulation. Alzheimer type II cells also manifest changes in the expression of gene coding for key astrocytic proteins. Type C HE is associated with significant neuronal cell death. Morphological changes, principally of brain astrocytes, are revealed during neuropathological examination.

Type A HE is observed in the presence of acute liver injury. It often progresses rapidly to coma, seizures, decerebrate rigidity and frequently to death. Cerebral edema is attributed in part to swelling of astrocytes. This type of HE is associated with a high mortality rate, and death is usually attributed to cerebral herniation and hypoxia caused by increased intracranial pressure. Causes include acetaminophen overdose and viral hepatitis.

In type B HE, toxins bypass the liver because of the artificial creation, congenital persistence or spontaneous development of portosystemic shunts, which connect the portal venous system supplying blood to the liver with the systemic venous circulation. Type C HE (more common than type B HE) is classed as episodic, persistent or minimal.

Main reason for introducing these descriptors was the widespread confusion in the literature over what constitutes acute or chronic HE. Most of the so-called chronic HE cases described in early reports were actually individual or recurrent episodes of HE in patients with chronic liver disease.

In patients with episodic HE, a disturbance of consciousness develops over hours to days, but does not persist. This is by far the most common form of HE. Episodic HE is usually marked by episodes of neuropsychiatric impairment precipitated by specific stimuli such as azotemia, the use of sedatives or tranquilizers, gastrointestinal bleeding, excess dietary protein, metabolic alkalosis, infections or constipation.

The category of episodic HE is divided into subcategories of precipitated, spontaneous and recurrent forms. Precipitated episodic HE is associated with specific causes (e.g., constipation, hyponatremia, sedative drugs, azotemia, hypokalemia, surgery) or factors that exacerbate liver damage (e.g., infection, an alcoholic binge) or increased blood concentrations of the products of protein metabolism (e.g., excessive dietary protein, bleeding in the gastrointestinal tract), whereas spontaneous episodic HE has no recognized precipitating factors. Recurrent HE is considered to be present when two bouts of precipitated or spontaneous episodic HE occur within a one-year period. In strictly defined persistent HE, neuropsychiatric deficits do not remit. Although fluctuations in the level of consciousness are observed, patients with persistent HE typically do not return to a normal mental status.

The working party recommends the West Haven Criteria (Table 1) and the Glasgow Coma Scale for assessing mental status in episodic or persistent HE. For minimal HE, the working party recommends the use of at least two of the following instruments: number connection test-A, number connection test-B, the block design test and the digit symbol test.

HE is divided into two primary components: overt HE (OHE) and minimal HE (MHE). It has been estimated that OHE is present in 30-45% of patients, with an annual risk of development in 20% of patients with cirrhosis.

### Table 1. West Haven Criteria for semiquantitative grading of mental status.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Trivial lack of awareness. Euphoria or anxiety. Shortened attention span. Impaired performance in addition.</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy or apathy. Minimal disorientation in time or place. Subtle personality changes. Inappropriate behavior. Impaired performance in subtraction.</td>
</tr>
<tr>
<td>3</td>
<td>Somnolence to semistupor but responsive to verbal stimuli. Confusion. Gross disorientation.</td>
</tr>
<tr>
<td>4</td>
<td>Coma (unresponsive to verbal or noxious stimuli).</td>
</tr>
</tbody>
</table>

Adapted from Ferenci, et al.³

### APPROACH FOR A PATIENT WITH CIRRHOSIS AND ALTERED MENTAL STATUS

During physical examination, a detailed evaluation of the vitals and airway should be performed at the outset and these should be managed accordingly. The physical examination should also concentrate on classifying the patient according to the West Haven Criteria. A focal motor deficit tends to be a global process. Patients with OHE may have
hyperreflexia, a positive Babinski’s sign and, in stages 2 and 3, asterixis, which may be demonstrated in the tongue and the upper and lower extremities. Asterixis is not specific for HE. If the above signs are evident, then the diagnosis of HE is fairly certain clinically and there is no need for further expensive imaging or psychometric and neurophysiological testing.

**APPROACH FOR A PATIENT WITH CIRRHOSIS AND NORMAL MENTAL STATUS**

Patients in this condition have been the focus of several recent investigations because the diagnostic methods used for cognitive evaluation in this population are varied and there is no consensus regarding the optimal strategy.

**Neuropsychometric testing**

The Portosystemic Encephalopathy Syndrome Test used by Weissenborn, et al. has been validated for MHE diagnosis in Germany, Italy and Spain. The Portosystemic Encephalopathy Syndrome Test is comprised of five tests:

- Number connection test-A (NCT-A).
- Number connection test-B (NCT-B).
- The line tracing test for errors and time.
- The serial dotting test.
- The digit symbol test (DST).

The cutoff value between normal and pathological was found to be 4 points, which resulted in a sensitivity of 96% and a specificity of 100%. Although the working group on HE recommends this test, it has not been validated for the USA. If it is not available, an option is to use a combination of two of the following four tests: the NCT-A, NCT-B, DST and block design test.

**Neurophysiological testing**

Neurophysiological tests are conducted under the supervision of a neurologist and require specialized equipment, personnel and time. These tests can therefore be difficult to administer in a regular clinical setting, although they are ideal for research settings. A test that is applicable to the clinical setting and does not require psychological expertise is the critical flicker frequency (CFF) test, which assesses the functional efficacy of the cortex, which has a direct correlation with psychometric abnormalities. Stepwise increments in light frequency from 25 Hz enable determination of the fusion–frequency threshold. A threshold of 38-39 Hz differentiates between manifest HE and subclinical or minimal HE. The benefits of this test are that it can be performed within a short period of time by clinic personnel without the need for a psychologist and that its cost is minimal.

The CDR test, developed by Cognitive Drug Research in the UK, consists of five psychometric subsets that test attention power, attention continuity, speed of memory and quality of episodic and working memory. The inhibitory control test (ICT) is a computerized variant of the continuous performance test that assesses sustained attention and response inhibition. It consists of 1,728 stimuli, 40 lures and 212 targets that are presented within 13 min after a training run. A high lure and a low target rate indicate poor psychometric performance. The ICT has been validated for the US population with 88% sensitivity for the diagnosis of MHE when a patient has had more than five lures.

**TREATMENT OPTIONS IN THE MANAGEMENT OF HEPATIC ENCEPHALOPATHY**

Treatment goals and options are dependent on the stage and severity of HE. The main goals are treatment of precipitating factors, improvement in mental status and evaluation of the possibility of a liver transplant, mainly in the context of an acute episode of HE. Outpatient management after an episode of HE consists of preventing recurrence of further episodes of HE, improving daily functioning and considering liver transplantation.

Ultimate management tool for OHE is a liver transplant. HE is a predictor of a poor prognosis for survival in patients with hepatopathy.

**Precipitating factors**

An extensive search for potential precipitating factors should be instituted along with treatment of OHE. Precipitants increase ammonia production or reduce the threshold for mental status decline, or produce a combination of these effects. The leading causes of OHE are gastrointestinal bleeding, sepsis and dehydration resulting from diuretics, diarrhea or vomiting. Another cause is nonadherence to medications. Ammonia levels are less informative than observation of a change in mental status in OHE and, therefore, may not predict or correlate
with actual clinical outcomes. Therapeutic options for HE are directed toward reducing ammonia production, increasing the fixation or excretion of ammonia, improving neurological function and modifying portosystemic collaterals. Lactulose is a nonabsorbable disaccharide that is fermented in the colon. Acidification of colonic contents and mass evacuation of bacteria have been proposed. The administration of lactulose when patients have been admitted with HE is associated with improved mental status, but it is difficult to pinpoint the reason for this improvement because precipitating factors are simultaneously being corrected. Lactulose should be administered in enema form to patients with stage 3 or higher OHE and should be given orally if the patient is able to tolerate it through this route.

Rifaximin is a nonabsorbable antibiotic that has been used to treat HE in several European countries. It has a favorable impact and the Cochrane review recommends its use. Prevention of recurrent episodes is key to normalization of daily functioning. A recent randomized trial demonstrated that lactulose therapy significantly reduced recurrent HE episodes after the first episode when compared with a placebo. A recent trial showed that rifaximin (550 mg BID) plus lactulose was significantly more effective than lactulose alone for prevention of HE episodes in patients who had experienced two or more HE episodes in the previous six months. According to the current guidelines, both drugs can be used for HE.

CONCLUSIONS

The recommendations of the working group for HE diagnosis and treatment provide a framework for further investigations aimed at refining diagnostic tests and developing clinically based treatments.

REFERENCES

20. Alcorn J. Review: rifaximin is equally or more effective than other antibiotics and lactulose for hepatic encephalopathy. ACP J Club 2008; 149(5): 11.