Hepatic encephalopathy syndromes

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Hepatic encephalopathy (HE) is a neuropsychiatric complication of acute and chronic liver failure. Its clinical spectrum ranges from minimal (subclinical) to overt encephalopathy. Psychometric and electrophysiological tests are helpful in diagnosing minimal HE. However, changes in metabolites in the brain, such as depletion of myo-inositol and accumulation of glutamine, appear to be very sensitive and specific in diagnosing this form. Positron emission tomography has been useful in studying brain ammonia metabolism. The main focus of medical treatment has been to modify ammonia metabolism. Reduction in ammonia production can be achieved by, among others, a diet rich in vegetable protein and carbohydrate, and oral lactulose, oral antibiotics and sodium benzoate. L-ornithine-L-aspartate provides critical substrates for both ureagenesis and glutamine synthesis, the key pathways for ammonia detoxification. Recent trials have shown its effectiveness in the treatment of HE. [Indian J Gastroenterol 2003;22(Suppl 2):S4-S6]

Key words: Ammonia, glutamine, liver transplantation, L-ornithine-L-aspartate, manganese, sodium benzoate

Hepatic encephalopathy (HE) syndrome is a neuropsychiatric complication of acute and chronic liver failure. There has been significant advance in its description especially related to its definitions, pathogenesis and pathology, but progress towards its treatment has been slow and unsatisfactory.

Nomenclature and definitions

HE reflects a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of other known brain abnormalities. The Working Party at the 11th World Congresses of Gastroenterology, Vienna, proposed a multiaxial definition of HE that defines both the type of hepatic abnormality and the duration/characteristics of neurological manifestations in chronic liver disease (Table 1).

<table>
<thead>
<tr>
<th>Type of hepatic abnormality</th>
<th>HE related to acute liver failure</th>
<th>Type of hepatic abnormality</th>
<th>HE related to portal-systemic bypass and no intrinsic hepatocellular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected subcategory</td>
<td>Subdivision</td>
<td>Affected subcategory</td>
<td>Subdivision</td>
</tr>
<tr>
<td>Minimal HE</td>
<td>Precipitated</td>
<td>Persistent HE</td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Severe</td>
</tr>
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<td></td>
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<td>Treatment-dependent</td>
</tr>
</tbody>
</table>

Table 1: Proposed nomenclature of hepatic encephalopathy

Type of hepatic abnormality: acute liver failure. Alternative term: type A (for acute liver failure).


- Encephalopathy associated with cirrhosis and portal hypertension and/or portal-systemic shunts. Alternative term: type C (for cirrhosis).

Duration/characteristics of neurologic manifestations in chronic liver disease

- Episodic HE. "A disturbance of consciousness that is accompanied by a change in cognition that develops over a short period of time and fluctuates in severity". It is further divided into HE episodes with (precipitated) or without (spontaneous) recognized precipitating factors. "Recurrent HE" is a term used when two episodes of episodic HE occur within one year.

- Persistent HE. This includes cognitive deficits that impact negatively on social and occupational functions.

- Minimal (subclinical) HE. The diagnosis is made in patients with chronic liver disease who do not demonstrate clinically overt syndromes of HE but present with abnormal neuropsychologic and/or neurophysiologic findings indicative of cerebral dysfunction. The term "minimal HE" is preferred over "latent" or "subclinical" HE because a majority of hepatologists believe that it impairs a patient's daily life and should be treated. Further, "subclinical" may mislead by indicating that the condition is below the threshold of significance.

The West Haven criteria for semiquantitative grading of mental state is the most acceptable (Table 2).

The clinical diagnosis of HE in patients with acute or chronic liver disease is easy. However, the clinician...
Table 2: West Haven criteria for semiquantitative grading of mental state

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

must not forget the following differential diagnoses: metabolic encephalopathy, toxic encephalopathy, intracranial lesions and neuropsychiatric disorders.

Investigations

Assessment of liver functions and appropriate biochemical tests to exclude the conditions listed in the differential diagnosis are essential. Important investigations for encephalopathy are as follows:

(i) Psychometric tests. These tests evaluate both cognitive and motor performance. Number connection test, figure connection test, block design test, digit symbol test, and reaction time to sound or light are important and sensitive psychometric tests.

(ii) Electrophysiological tests, including EEG and evoked responses, both in use for a long time.

(iii) Magnetic resonance imaging (MRI): Bilateral symmetry of hyperintensities in the globus pallidus on T1 weighted images is the most consistent finding. This is considered to be due to excess manganese deposition secondary to high blood levels caused by its impaired elimination in liver disease.

(iv) Magnetic resonance spectroscopy (MRS): Measures brain metabolites and metabolic rates of toxic substances such as ammonia and glutamine and the energy status in the brain of patients with liver disease and HE. An increase in the glutamine/glutamate peak coupled with a decrease in the myo-inositol and choline signal are the characteristic findings on "H spectra.

(v) Positron emission tomography (PET): Has been useful to study ammonia metabolism in liver disease and provides better understanding of the pathophysiology of HE.

(vi) Tests for toxic metabolites and enzymes, including ammonia, manganese, glutamates, lactate, etc.

Pathology and physiology

Astrocytes are the target cells for damage in HE while neurons are less affected. Astrocytes in HE secondary to portal-systemic shunting take a characteristic swollen shape and assume the form of Alzheimer type-2 glial cells. Their nuclei are enlarged, and cytoplasm contains excess glycogen. Brain edema and brain-stem herniation are the main morphological features of HE associated with fulminating hepatitis. Alzheimer type-2 change is not observed though swelling of astrocytes and astrocytic end feet is recorded by electron microscopic studies. Ammonia and manganese are the two main toxic substances related to the pathophysiology of HE. Deficit in neurotransmission and cerebral hypometabolism are the two complex processes in its pathophysiology. Down-regulation of glutamine receptors and increase of inhibitory neurotransmission by gamma aminobutyric acid through a mechanism involving benzodiazepine and its receptors results in a shift in the balance between inhibitory and excitatory neurotransmission. In contrast, brain edema in HE due to acute liver failure is primarily due to the cytotoxic effects of glutamine secondary to its accumulation within astrocytes. Alteration in cerebral blood flow also contributes to the development of cerebral edema.

Despite over 20 toxins reported in HE, ammonia remains the most important agent in the pathogenesis of the adverse biochemical events. Manganese is also an important toxic factor. Mn is excreted by the hepatobiliary route and its blood concentration is increased in cirrhosis. Deposition of manganese in the globus pallidus affects both the glutamatergic system and cerebral energy metabolism. Manganese affects astrocyte function and morphology, which contributes to HE. Serotonin, catecholamines, and opioid systems also alter the neurotransmitter systems, but their role is not as significant as that of ammonia and manganese.

Management

Medical treatment has not been effective in improving the short- and long-term prognosis of patients with acute and chronic liver disease with HE.

Restricted-protein diets were recommended in the 1950s. The European Association for Enteral and Parenteral Nutrition in 1997 changed this. Protein intake of 1 to 1.2 g/Kg is now recommended. However, studies have shown that this recommendation is infrequently followed. The main focus of medical treatment has been to modify ammonia metabolism. Reduction in ammonia production can be achieved by an appropriate diet rich in vegetable protein and carbohydrate, along with oral lactulose, oral antibiotics, sodium benzoate, and sodium phenylacetate. L-Orithine-L-aspartate provides critical substrates for both ureagenesis and glutamine synthesis, the key pathways for ammonia detoxification. Recent trials have shown that lowering of blood ammonia and improvement in HE can be achieved by this approach. Experimental studies support these conclusions. L-Carnitine has also been shown to have...
beneficial effects in preventing ammonia-precipitated HE.23

The benzodiazepine-receptor antagonist flumazenil and dopamine agonist L-dopa have been used in clinical trials but their therapeutic value is doubtful. The neurotransmitter system is open for attack by newer drugs. Both agonist and antagonist drugs are under trial. A few of them, such as methysergide and melitpepine, have been used in animal studies.24 Antagonists to the NMDA glutamate receptor are under investigation. Chelation therapy with calcium edetate and treatment with sodium para-aminosalicylic acid have been used in manganese toxicity and deserve trial in HE.25 Future options are promising, but at present solutions are disappointing.

Liver transplantation

Liver transplantation is increasingly and successfully being done for acute and chronic irreversible diseases of the liver. In fact, in many countries medical treatment is restricted to those who cannot be transplanted. One report noted that the 1- and 3-year survival of transplanted patients was 80% and 70%, respectively, while the corresponding figures for medically treated patients were 73% and 38%, respectively. However, until a transplantation program is established in India we will have to focus on improving the results of medical management.

References


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