Assessing the severity of hepatic encephalopathy

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The diagnosis of hepatic encephalopathy (HE) is based mostly on clinical criteria. It is important to assess the severity of HE quantitatively for both clinical practice and research; however, this remains a difficult and challenging problem. Modalities like psychometric tests, electroencephalography, evoked potentials, and several innovative biochemical indices have shown promise in this regard. No single parameter or index has yet been shown to be infallible in assessing the severity of HE. [Indian J Gastroenterol 2003;22(Suppl 2):S7-S10]

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Comprehensive assessment of patients with disorders of consciousness is a difficult and challenging problem. Hepatic encephalopathy (HE) is no exception. The clinical profile of HE includes a wide range of neuropsychiatric symptoms, from minor, difficult-to-discriminate signs of altered brain function to overt psychiatric and neurological presentations or deep coma. None of these is, however, specific for HE. There is a clear need for quantitative assessment of the severity of HE, not only to document response to therapy and to prognosticate survival, but also in order to assess the impact of newer therapeutic strategies.

Since the days of Morgagni’s description of HE and his explanation on the basis of “constriction of hepatic nerves by passions of the mind” in his 17th century treatise, The Seats and Causes of Disease, we have come a long way in our understanding of this clinical entity. However, assessment of the severity of HE still remains mainly clinical, as is its diagnosis.

Clinical grading

The simplest grading of HE is based on clinical findings. The West Haven criteria that grade HE from grade 1 to 4 are based on changes of consciousness, intellectual function, and behavior. For stages 3 and 4, the Glasgow Coma Scale is an additional useful clinical parameter that measures the response to eye opening, verbal behavior, and motor responsiveness, qualifies neurologic impairment, and is less subject to observer variability than evaluation of consciousness.

Psychometric tests

Psychometric tests were designed to document and measure subtle worsening or improvement of HE. Simple tests like drawing figures, serial 7s, and recall of current events lack precision and are not easily quantifiable.

Detailed psychometric tests are sensitive in detecting minor defects of mental function. The most frequently applied test is the number connection test or Reitan test. This consists of a series of numbers, or numbers and letters, to be connected in order by a continuous line. The time taken to complete this test is recorded (Table 1). Errors are not counted. This test can be easily administered and the results obtained quickly. (Various psychometric tests have been discussed elsewhere in this issue.)

Electroencephalography

Any functional impairment of the brain results in changes in its electrical activity and thereby in the electroencephalogram (EEG). Initial EEG changes in HE consist of a bilaterally synchronous decrease in wave frequency, increase in wave amplitude, and disappearance of normal alpha rhythm. Preterminally, there is loss of wave amplitude and triphasic waves; this occurs characteristically in stage 3 HE. However, these EEG changes including the triphasic waves are non-specific and have been described in other metabolic encephalopathies too.

The simplest EEG assessment of a patient in HE is to grade the degree of abnormality of the conventional EEG trace (Table 2). Automated EEG analysis using

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Table 1: Assessment of Number Connection Test A

<table>
<thead>
<tr>
<th>Grade of abnormality</th>
<th>Time taken (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15-30</td>
</tr>
<tr>
<td>1</td>
<td>31-50</td>
</tr>
<tr>
<td>2</td>
<td>51-80</td>
</tr>
<tr>
<td>3</td>
<td>81-120</td>
</tr>
<tr>
<td>4</td>
<td>&gt;120 (unable to perform test)</td>
</tr>
</tbody>
</table>

Table 2: Grading of abnormalities in electroencephalogram in hepatic encephalopathy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Generalized suppression of alpha rhythm</td>
</tr>
<tr>
<td>B</td>
<td>Unstable alpha rhythm with paroxysmal waves 5 to 7 per second, occasional underlying fast activity</td>
</tr>
<tr>
<td>C</td>
<td>Runs of medium voltage, 5 to 6 per second waves bilaterally over frontal and temporal lobes; alpha rhythm seen occasionally</td>
</tr>
<tr>
<td>D</td>
<td>Constant 5 to 6 per second waves in all areas</td>
</tr>
<tr>
<td>E</td>
<td>Bilaterally synchronous, 2 to 3 per second waves predominantly over frontal lobes and spreading backwards to occipital lobes, occasional short-lived appearance of faster rhythm (5 to 6 per s)</td>
</tr>
</tbody>
</table>
computer-assisted techniques that allow quantitation of abnormalities is a more refined method. It reveals changes in the mean dominant EEG frequency and relative powers of delta and theta bands and appears to be useful in the objective classification of the severity of HE (Table 3) and in detection of subclinical HE. Computed spectral analysis performed by dominant frequency and occipital alpha-theta ratio expressed as its logarithmic transformation has been shown to correlate with Child score and presence of HE.

Ammonia levels

Although there is little doubt that ammonia plays an important role in the pathogenesis of HE, the relationship between plasma ammonia and the severity of cerebral dysfunction is variable. Many investigators have described a close relationship between ammonia levels and cerebral function, but others have questioned its existence. Use of venous ammonia levels, which are appreciably lower than arterial ammonia to which the brain is exposed, may account partly for these discrepancies. Arterial ammonia levels are measured by an enzymatic method and severity is graded according to the measured level (Table 4).

Arterial pH-dependent partial pressure of gaseous ammonia (pH₄) has been found to correlate more closely with the degree of clinical and neuropsychological abnormalities in HE than total arterial ammonia levels, and may thus be a better method for evaluation of HE. Breath ammonia levels have also been recently shown to correlate with blood ammonia and show promise as a non-invasive tool in the assessment and follow up of patients with HE.

Portosystemic encephalopathy index (PSEI)

A PSEI consisting of mental status, except for the addition of a grade 0 where no abnormality was found, arterial ammonia (as in Table 4), EEG (as in Table 3), the number connection test (as in Table 1) and degree of

| Table 3: Assessment by automated electroencephalography using mean dominant frequency |
|---|---|
| Grade | Mean dominant frequency (cycles/second) |
| 0  | Normal alpha rhythm (less than 12) |
| 1+ | 7 to 8 |
| 2+ | 5 to 7 |
| 3+ | 3 to 5 |
| 4+ | Less than 3 |

| Table 5: Assessment of asterixis |
|---|---|
| Grade | Finding |
| 0  | No flapping motion |
| 1+ | Rare flapping motion (1-2 per 30 seconds) |
| 2+ | Occasional, irregular flaps (3-4 per 30 seconds) |
| 3+ | Frequent flaps (5-30 per 30 seconds) |
| 4+ | Almost continuous flapping motions |

(Presence of asterixis determined by extending patient’s arms and forearms with wrist dorsiflexed for at least 30 seconds)

Asterixis (Table 5) was developed as a composite score for assessing the severity of HE. In doing so, an arbitrary weight of 3 is assigned to mental status, whereas other parameters are given a weight of 1 each. Thus mental status has a maximum potential score of 12 compared to 4 for the other parameters. The sum of the weighted scores, with a possible maximum of 28, is called the PSEI sum. PSEI scores are not always comparable at some tests like number connection test, asterixis and EEG may not be possible in all patients. The PSEI is calculated as the ratio of the PSEI sum to the highest possible PSEI sum for the particular patient. Thus, if one or more components are not tested, then the score for those components are not included in the denominator and the PSEI is based only on the gradable components. The PSEI Efficacy Index is calculated as the ratio of the improvement in PSEI after therapy to the PSEI before therapy. It permits a comparative evaluation of PSEI in different treatment groups.

PSEI has been used extensively for several years. However, concern has been raised about the significance given to arterial ammonia, which has not been shown to correlate with the severity of HE. Fixed normal values for the number connection test, mixing clinical symptoms with proposed pathogenetic factors, and the need for repeated arterial punctures or placement of an arteria line for measuring ammonia levels are other potential limitations of this index. Recently, the US FDA has stipulated that the time-honored PSEI index is no longer acceptable as a major end point of efficacy in treatment of HE.

Evoked responses

Somato-sensory evoked potentials (SSEP), in particular its late component, and visual evoked potentials (VEP) have been considered useful in the evaluation of HE. The N1-N3 interpeak latency on SSEP has been found to correlate with the clinical stage of HE. The changes in SSEP are reversible and have been found to be useful in monitoring effects of treatment in patients with HE. Four different patterns of the VEP waveform have been described in patients with HE; these correlate with clinical stages of HE and the degree of EEG abnormalities.

The auditory and visual event-related potential is thought to be a useful parameter for assessing cognitive function disorders and considered to be the elec-
trophophysiological counterpart of the psychometric tests as both involve active use of the cognitive faculties. Since recording of both auditory and visual event-related potential needs skilled operators and patient's cooperation, these techniques are limited to a few centers and to patients with mild HE.

**Intracranial pressure monitoring**

The value of intracranial pressure (ICP) monitoring in the assessment of severe HE is controversial. Raised ICP, probably due to cerebral edema, is an important complication of fulminant hepatic failure (FHF) and may be a principal cause of death in a large proportion of patients with FHF.  

ICP monitoring and its usefulness have been discussed elsewhere in this issue.

**Non-invasive imaging**

Computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and single photon emission computed tomography (SPECT) have all been studied in patients with HE. CT and MRI show frontal lobe atrophy in some patients with subclinical HE. Pallidal hyperintensity on T1-weighted MRI has been shown to correlate with blood ammonia levels and the presence but not the grade of HE. Reduction of regional blood flow in the hippocampus in patients with subclinical HE has been noted by SPECT, and this correlates with degree of abnormalities in neuro-psychological tests. Reduction in the concentrations of myo-inositol and choline and elevation of those of glutamine and glutamic acid at MRS in the cerebrum of patients with subclinical HE and overt HE, also closely correlate with the results of quantitative neuro-psychological tests. A more recent study, however, suggested that changes in MRS are unlikely to reflect the severity of HE, but rather represent the chronic metabolic derangement of the brain associated with decreased hepatic functional reserve.

**Other biochemical parameters**

Serum amino acids, plasma and brain quinolene acid, plasma benzodiazepine receptor ligand concentration and serum levels of astrogial S100 beta are among the more esoteric indices of severity of HE that have found mention in medical literature. These indices, however, have not been used subsequently in the assessment of severity of HE.

A good correlation has been found between the cerebrospinal fluid concentrations of glutamic acid and alpha-ketoglutaramate and the degree of HE; however, the presence of raised ICP and coagulopathy restricts the use of lumbar puncture in patients with HE.

**Conclusions**

No single parameter or index has been shown to be infallible in assessing severity of HE. Clinical assessment alone misses out subclinical encephalopathy. No single biochemical parameter correlates reproducibly with severity of HE. PSEI, a combined scoring system based on several parameters, too has major limitations. A statistically and clinically validated index, which is simple, reliable, standardized, easily reproducible, and does not require patient cooperation, is needed for assessment of patients with HE, especially for clinical trials.

**References**


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