UPDATES IN THE PATHOGENESIS AND DIAGNOSIS OF HEPATIC ENCEPHALOPATHY

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UPDATES IN THE PATHOGENESIS AND DIAGNOSIS OF HEPATIC ENCEPHALOPATHY (Abstract): In the pathophysiology of hepatic encephalopathy (HE), a serious complication of liver cirrhosis, different hypotheses, including increased blood ammonia levels, increased production and absorption of intestinal bacterial products are discussed. Recent studies demonstrated that Helicobacter pylori infection is associated with elevated blood ammonia levels. Inflammatory mediators and cytokines also play important roles along with hyperammonia in the pathogenesis of HE, while recent studies revealed correlations between CRP levels and length of hospital stay. Neuropsychological diagnostic tests, such as Psychometric Hepatic Encephalopathy Score, were especially designed for detecting minimal HE. Imaging investigations, like Computed Tomography or Magnetic Resonance Imaging, show characteristic aspects in advanced stages of liver disease. Recent studies revealed that Mini-Mental State Examination (MMSE) can show significant changes mostly in advanced stages of overt HE, but that it is not an appropriate tool in defining an encephalopathy-related status of patients with cirrhosis. Keywords: HEPATIC ENCEPHALOPATHY, LIVER CIRRHOSIS, PATHOGENIC

Cirrhosis represents the end-stage of chronic liver disease from any cause. In the natural history of liver cirrhosis there is a compensated phase (i.e. asymptomatic phase), followed by a decompensated phase, defined by the development of complications, such as portal hypertension and/or liver insufficiency, specifically ascitis, variceal hemorrhage, and/or encephalopathy (1). Hepatic encephalopathy (HE) is a serious complication of liver cirrhosis, negatively affecting both health-related quality of life and survival. Although it is now considered as a continuum of neurocognitive deterioration, HE is usually divided into minimal and overt HE according to mental status change. In minimal HE characteristic are the lack of a detectable brain dysfunction at clinical examination but subclinical psychomotor slowing and cognition deficits are present and clinically relevant. Overt HE is characterized by various symptoms encompassing neuromuscular abnormalities, disorders in intellectual functions, personality and consciousness, traditionally graded in four stages, after West-Haven criteria (2).
PATHOPHYSIOLOGY

HE is a multifactorial syndrome, involving metabolic and biochemical derangements, brain atrophy and edema, impaired cerebral perfusion and hyperpermeability of blood-brain barrier (3). HE occurs in the presence of insufficient hepatic clearance of toxins absorbed from the intestine, resulting in neurochemical abnormalities across the blood-brain barrier.

Specific hypothesis of HE

Ammonia

Cirrhosis represents the final common histological pathway for a wide variety of chronic liver diseases. The blood ammonia levels of cirrhotic patients are usually higher than that of normal people (4).

Ammonia is central in the disease process, contributing to alterations in neurotransmission, oxidative stress, cerebral edema and astrocyte swelling (5). This compound is mainly derived from nitrogenous products in the diet, bacterial metabolism of urea, and deamination of glutamine by the enzyme glutaminase. Ammonia enters the portal circulation from the gut and is converted to urea in the liver. In the presence of significant portosystemic shunting, with or without hepatocellular dysfunction, ammonia concentration rises in blood and crosses the blood-brain barrier. Exposure to increased brain ammonia results in structural alterations in astrocytes that cause swelling and brain edema. Over a long period of exposure to high ammonia levels, astrocytes develop structural changes, known as Alzheimer type II astrocytes (6).

New studies show roles of changes in active glutamine transport in brain edema development during HE. Excessive glutamine (Gln) synthesis in ammonia-overloaded astrocytes contributes to astrocytic swelling and brain edema. Much of the newly formed Gln is believed to enter mitochondria, where it is recycled to ammonia, which causes mitochondrial dysfunction (a “Trojan horse” mode of action). A portion of Gln may increase osmotic pressure in astrocytes and the interstitial space, directly and independently contributing to brain tissue swelling. Accumulation of excess Gln in mitochondria involves a carrier-mediated transport which is activated by ammonia. Excessive synthesis of Gln from ammonia and glutamate catalyzed by an astrocyte-specific enzyme, glutamine synthetase (GS) plays a major role in the pathogenesis of astrocytic swelling (7).

Bowel Bacterial Overgrowth

According to previous studies, the patients with liver cirrhosis have an increase in production and absorption of intestinal bacterial products, which can lead to a continuous flux of lipopolysaccharides and other toxic materials to the portal vein. In the liver, these substances are recognized by Kupffer cells and thus trigger the release of tumor necrosis factor (TNF), which, together with other products of these cells, leads to hepatocyte lesion (8).

Compounds derived from bacterial activities in the gut can cause neurochemical changes in the brain. These gut-derived toxins (e.g., ammonia, benzodiazepine-like substances) are implicated in the pathophysiology of overt HE. In patients with liver disease or portosystemic shunting, these toxins are inefficiently detoxified, accumulate in the blood, cross the blood-brain barrier, and result in abnormalities, such as altered neurotransmission, astrocyte swelling, and impaired energy metabolism (9).

Helicobacter pylori

Not only bowel bacterial overgrowth must be discussed as an oligosymptomatic
cause of HE, but other bacterial infections in cirrhotic patients might be important, such as *Helicobacter pylori* infection. *H. pylori* infection can produce high blood ammonia concentration in these patients (8).

*H. pylori*, a bacterium which commonly infects human stomach, has urease activity, which is many times more potent than that of enterobacteria. The *H. pylori* urease in the gastric juice breaks down urea into ammonia and carbon dioxide, and the ammonia is then rapidly absorbed into the blood (4).

From thirteen prospective clinical trials which assessed the effects of *H. pylori* eradication in patients with liver cirrhosis and HE, seven of these showed a beneficial effect of eradication therapy on minimal HE. All of these studies were highly diverse in design and methodology (10). Eradication therapy in *H. pylori*-positive cirrhotic patients may have a beneficial influence on hyperammonemia and minimal HE, but evidence from well-designed clinical studies is weak (10).

**Inflammation**

It is now clearly evident that inflammatory mediators and cytokines play an important role along with hyperammonia in the pathogenesis of HE; possible mechanisms include cytokine-mediated changes in blood-brain barrier permeability, microglial activation, subsequent production of neurosteroids, and altered activity of peripheral benzodiazepine binding sites (6).

Inflammation in the presence of ammonia coactively worsens HE. Inflammation can result from hyperammonemic responses, endotoxemia, innate immune dysfunction or concurrent infection. Treatments currently focus on reducing inflammation and/or blood ammonia levels and provide varying degrees of success (5). It has been shown that the high correlation between CRP levels and the total in-hospital days corroborates the impact of the systemic inflammatory status, not only at the moment of hospital arrival, but also as an indicator of HE regression during the treatment with antibiotics (8). Other studies correlates the CRP levels with encephalopathy occurrence in cirrhotic patients, and many others have described the relevance of inflammation in HE neural physiology. These studies demonstrate for the first time that CRP levels are correlated with the hospitalization duration (11, 12, 13). The role of inflammatory cytokines in affecting the blood–brain barrier and increasing the ammonia diffusion in astrocytes was also well described by other authors. In conclusion, CRP reduction must be a clinical target during antibiotic treatment in HE when the values obtained are high (8).

**Hyponatremia**

In a recently observational study, it has been shown that hyponatremia was a common feature in patients with liver cirrhosis and its severity increased with the severity of liver disease. The existence of serum sodium concentration < 135 mmol/L was associated with greater frequency of HE compared with patients with serum sodium concentration > 135 mmol/L (14).

**Other mechanisms for HE**

- Increased benzodiazepine-like compounds in the brain.
- Accumulation of manganese in the basal ganglia: this is implicated in altered dopaminergic neurotransmission and extrapyramidal symptoms.
- Alterations in central nervous sys-
tem (CNS) tryptophan metabolites (e.g. serotonin): these changes may underlie some of the classic descriptions of altered sleep-wake cycles seen in early stages of encephalopathy (6).

**DIAGNOSTIC OF HE**

The diagnosis of HE first requires excluding other potential causes for encephalopathy. Metabolic disorders, infectious diseases, intracranial vascular events, and intracranial space-occupying lesions can present with similar neuropsychiatric symptoms and need to be excluded (15). Consideration of the possibility of HE arises when significant liver dysfunction is known or suspected to be present. Clinical or laboratory evidence of liver failure and/or portal hypertension is usually obvious (6).

The West-Haven grading system (table I), which classifies HE into categories, remains criticized because of its intense subjectivity and low intra- and inter-observer reliability. Therefore, several other more objective diagnostic tools (e.g. neuroimaging, neurophysiological methods or psychomotor tests), were implemented to diagnose both minimal and overt HE, but there is still an ongoing debate which of them should be a diagnostic standard (2).

**TABLE I**

**West Haven criteria for classification of hepatic encephalopathy (6)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Recommended Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No abnormality detected</td>
<td></td>
</tr>
<tr>
<td>Covert HE</td>
<td>Normal mental status and neurologic examination Abnormal psychometric tests</td>
<td>&gt;2 SD on 2 or more tests in PHES ICT: &gt;5 lures CFF: cutoff frequency 39 Hz</td>
</tr>
<tr>
<td>I</td>
<td>Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction</td>
<td>Naming &lt;= 7 animals in 120 sec Orientation in time and space</td>
</tr>
<tr>
<td>II</td>
<td>Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior</td>
<td>Disorientation in time (&gt;/=3 items incorrect): ✓ Day of the week ✓ Day of the month ✓ The month ✓ The year Orientation to place</td>
</tr>
<tr>
<td>III</td>
<td>Somnolence to semistupor Responsiveness to stimuli Confusion Gross disorientation Bizarre behavior</td>
<td>Disorientation to place (&gt;/=2 items incorrect): ✓ State/country ✓ Region/country ✓ City ✓ Place ✓ Floor/ward Disorientation to time Reduction of Glasgow coma score (8-14)</td>
</tr>
<tr>
<td>IV</td>
<td>Coma, inability to test mental state</td>
<td>Unresponsiveness to pain stimuli (Glasgow coma score &lt;8)</td>
</tr>
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CFF, Critical Flicker/Fusion Frequency; HE, hepatic encephalopathy; ICT, Inhibitory Control Test; PHES, Psychometric Hepatic Encephalopathy score; SD, Standard deviation.

1. **Blood ammonia**. No significant cor-
Updates in the pathogenesis and diagnosis of hepatic encephalopathy

Relation between serum ammonia level and stage of HE has been observed. Most authors agree that measurement of ammonia may be helpful in the initial evaluation of unexplained encephalopathy in patients with not known prior history of liver disease. Normal ammonia values in these patients would argue against a diagnosis of HE (15).

Measurement is not recommended routinely, because it does not change the approach to diagnosis or treatment of patients with suspected HE (6). The measurement of serum ammonia levels for the diagnosis of HE remains controversial: some authorities consider that the use of arterial blood is preferred (15), while others consider that venous ammonia level correlates with the severity of HE as arterial ammonia level does (3).

2. Psychometric testing. Neuropsychological diagnostic tools show a number of practical advantages, making them potent candidates for the common use in HE assessment. Generally, they are simple to perform, not time-consuming and can be used in the outpatient clinic. For this purpose, both single paper-pencil tests (such as the block design test, the trail making test and the digit symbol test), as well as standardized batteries (i.e. the Repeatable Battery for the Assessment of Neuropsychological Status, the Wechsler Adult Intelligence Scale - Revised, the Auditory Verbal Learning, the Everyday Memory Questionnaire) have been implemented. The complex tools have a superior value in comparison to single modalities, because they cover a broad spectrum of neurocognitive deficits. However, among plenty of these tests, only the Psychometric Hepatic Encephalopathy Score (PHES) was especially constructed for detecting minimal HE. Others have a great importance in the diagnostic of cognitive alteration in elderly or neuropsychiatric disorders, in the estimation of the effects of psychoactive drugs or to measure intelligence, while their value in the field of HE remains to be established (2).

Critical Flicker/Fusion Frequency (CFF) test - is based on the hypothesis that retinal gliopathy (hepatic retinopathy) could serve as a marker of cerebral gliopathy in HE. It correlates well with paper and pencil psychometric tests used to diagnose covert HE. It enables discrimination of stage 0 HE from covert HE and overt HE at a cutoff frequency of 39 Hz, with a sensitivity of 55% and a specificity of 100%. It is useful for monitoring fluctuations in the severity of HE in response to precipitating factors or therapeutic interventions (6).

3. Electroencephalography (EEG) - is rarely used clinically, it has some value in research settings (6). It is often performed in patients with their first presentation of HE or in any patient in whom the presentation is atypical in nature. The EEG may have some value in determining the advanced stages of HE, when characteristic triphasic waves are identified (15).

However, the EEG detects cortical neuronal activity and may not reflect a wide variety of neurophysiological events seen in HE. Moreover, it is not broadly implemented in the daily practice, because of its limited availability and the need of experienced personnel to appropriate interpretation of the obtained electroencephalograms (2).

4. Computed tomography (for porto-systemic shunts)

Cirrhotic patients with persistent or recurrent HE commonly have large spontaneous portal-systemic shunts. Using multidetector computed tomography (CT) imag-
ing, it has been shown that large spontaneous porto-systemic shunts are significantly more common in patients with (71%) than without (14%) HE. This approach is ideal in patients with compensated liver disease, where signs and symptoms suggest HE, but the severity of liver disease is mild (15).

5. **Magnetic resonance imaging (MRI).** MRI has become a standard technique for the assessment of patients with neurologic manifestations. Patients with liver cirrhosis and no clinical manifestations of HE can have symmetrical high-signal abnormalities in the pallidum on T1-weighted images. Pallidal hyperintensity is not related to the grade of HE; rather, its absence in a patient with cirrhosis and neurologic manifestations suggests an alternative diagnosis. Decreased brain myo-inositol and elevated glutamine by magnetic resonance spectroscopy is characteristic of HE when detected (15).

6. **Mini-Mental State Examination (MMSE)** is one of the most commonly used methods in the assessment of cognitive mental status. MMSE is one of above mentioned complex neuropsychological tools, that was occasionally used for identification patients with HE in clinical trials and could serve as a potential screening test for this purpose. MMSE assesses cognitive abilities: orientation (spatial and time), attention, concentration, calculation, immediate and short-term memory, visual-spatial orientation, praxis and language skills. Some of these functions are also altered in cirrhotic patients in the course of minimal HE and in stages 1 and 2 overt HE according to West-Haven criteria, long before neurocognitive decline is obvious and clinically easy to detect (2).

In a prospective, quantified electroencephalography study, the authors concluded (2) that MMSE is not an appropriate tool in defining an encephalopathy-related status of patients with cirrhosis and should not be used for this purpose in clinical trials. The authors showed that the score (summary scores and most of the items) is altered in patients with more advanced liver disease measured by Child-Pugh classification and there is a reduction of the most of MMSE items in patients with overt HE, but differences reached the statistical significance only in few items and mostly in more advanced stages of overt HE (i.e. in grade 2 and 3) and the numeric difference between MMSE scores was small and unlikely to be clinically useful.

**CONCLUSIONS**

Hepatic encephalopathy (HE) is a serious complication of liver cirrhosis, involving metabolic and biochemical derangements, brain atrophy and edema, impaired cerebral perfusion and hyperpermeability of blood-brain barrier. In the pathophysiology of this complication, different hypotheses, including increased blood ammonia levels, increased production and absorption of intestinal bacterial products, *Helicobacter pylori* infection which can produce high blood ammonia levels are discussed. Inflammatory mediators and cytokines also play important roles along with hyperammonia in the pathogenesis of HE, while recent studies revealed correlations between CRP levels and length of hospital stay. Of the diagnostic tools for HE, the measurement of serum ammonia levels remains controversial, because no significant correlation were found between serum ammonia level and HE stage. Of the neuropsychological diagnostic tests, only the Psychometric Hepatic Encephalopathy Score (PHES) was especially designed for
detecting minimal HE. Imaging investigation, such as CT or MRI, show characteristic aspects in advanced stages of liver disease. Also, recent studies revealed that MMSE is not an appropriate tool in defining an encephalopathy-related status, significant changes being found mostly in more advanced stages of overt HE.

In view of the complex aspects in the pathogenesis and diagnosis of HE, there is still a need for developing more specific tests for an objective evaluation of the entire spectrum of this complication, better management and treatment.

REFERENCES