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Original Research Article

Concise review of current concepts on nomenclature and pathophysiology of hepatic encephalopathy

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ARTICLE INFO

Article history:
Received 12 December 2013
Accepted 24 April 2014
Available online 27 June 2014

Keywords:
Encephalopathy
Cirrhosis
Pathogenesis

ABSTRACT

Hepatic encephalopathy is a neuropsychiatric complication of liver cirrhosis the symptoms of which may vary from imperceptible to severe, invaliding, and even lethal. Minimal hepatic encephalopathy is also important because of its tendency to impair patients' cognitive functions and quality of life.

The polyetiological pathogenesis of hepatic encephalopathy is intensively studied. A general consensus exists that not only excess of ammonia but also inflammatory, oxidative, and other processes are significant in the development of hepatic encephalopathy.

1. Nomenclature of hepatic encephalopathy

The first who clearly and contemporary described the clinical symptoms of hepatic encephalopathy (HE) was Frerichs [1]. For the evaluation of HE severity in clinical studies and clinical practice, West Haven's criteria and Glasgow coma scale still are most widely used.

Since the assessment of patients with mild HE strongly relies on subjective impression of physician a gradation of HE with reference to hospitalization necessity was proposed: low-grade HE without hospitalization necessity (Grade 0–II West-Haven) and high-grade HE with obligatory hospitalization (Grade III–IV West-Haven) [2]. The most recent continuous HE classification was suggested by members of International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) [3]. This group has suggested to classify HE according to worsening of cognitive function from unimpaired (without any clinical, neurophysiological or neuropsychometric changes) to covert (minimal HE and Grade I according West-Haven) and overt (Grade II according West-Haven) [3].

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Peer review under the responsibility of the Lithuanian University of Health Sciences.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.medici.2014.06.008

Table 1 – West Haven's criteria.

Grade	Criteria
Grade 0	Lack of detectable changes in personality or behavior No asterixis
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition Asterixis may present
Grade 2	Lethargy or apathy Minimal disorientation for time or place Inappropriate behavior Subtle personality Slurred speech Impaired performance of subtraction
Grade 3	Somnolence to semistupor, but responsive to verbal stimuli Confusion Gross disorientation Asterixis is usually absent
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Adapted from Mulen KD.

West Haven's criteria [4] distinguished four grades of HE according to expression of mental status impairment, persistent tremor starting with the less expressed (Table 1) [5]. The Glasgow coma scale (GCS) independently evaluates eye opening (E), verbal performance (V) and motor responsiveness (M) dysfunctions in grades starting with the most severe [6]. A total GCS grade is calculated as a sum of those three aspects of behavior (E + V + M). GCS grade ≤8 is treated as severe brain injury, GCS grades 9–12 – as moderate brain injury and GCS≥13 – as minor one.

There are several more HE validation and classification methods suggested, such as the Hepatic Encephalopathy Scoring Algorithm (HESA), the Clinical Hepatic Encephalopathy Staging Scale (CHESS) and the Porto-Systemic Encephalopathy (PSE) index. The HESA validates mental status and neuropsychological parameters, while PSE index evaluates EEG and blood ammonia in addition to clinical parameters [7]. The CHESS consists of 9-question scale which allows evaluating orientation and current awareness. This scale was suggested by Ortiz et al. [8] and lets easily verify clinical stage of HE (from normality – 0 to coma – 9).

All mentioned above HE scoring systems, except West Haven's criteria, are not properly evaluated and still not widely used in clinical practice [9].

The currently accepted definition and classification of HE was approved at the 11th World Congress of Gastroenterology in Vienna, Austria in 1998 [7]. HE was defined as a spectrum of neuropsychiatric abnormalities seen in patients with chronic liver disease after exclusion of other known brain disorders.

Based on liver damage, three types of HE were defined in the Final report of the 1998 Working Party [1]: A type is associated with acute liver failure, [2] B type is associated with portosystemic shunts without parenchymal liver diseases, and [3] C type is associated with liver cirrhosis and portal hypertension or portosystemic shunts [7].

By characteristics and duration of symptoms, B and C types of HE may be episodic, persistent, and minimal [5,10].

- Episodic HE develops in hours or days, though patients recover to previous state. Episodic HE may be precipitated (caused by provocative factors such as gastrointestinal bleeding, diuretics overdose, constipation, electrolytes disbalance, sedatives, dehydration, alcohol consumption, infection, excessive amount of proteins in food), spontaneous (with no definite provocative factor), and recurrent (recurring not less than twice per year).
- Persistent HE clinical manifestation varies from subtle cognitive abnormalities to significant mood swings, sleep disturbances, stupor, and coma. According to the degree of autonomy impairment Working Party participants had proposed to subdivide persistent HE in mild (grade I by West Haven's criteria) severe (grades II–IV) and treatment-depended [7].

Allocation of the treatment-depended HE in separate subgroup was not sufficiently reasoned by Working Party participants but still is widely used. This subgroup was defined on the basis of recurrence of HE symptoms immediately after treatment discontinuation. The overt HE symptoms can occur regardless HE severity, so we tend to exclude treatment-depended HE subgroup from the persistent HE subdivisions and are likely to be limited to two subgroups: mild and severe (Table 2).

Mentioned above statements are useful for the evaluation of severity of clinically manifested HE, but not helpful much in case of MHE. In this particular HE stage a cirrhotic patient's mental status can be considered as normal, but

Table 2 – Nomenclature of hepatic encephalopathy (HE).

Type	Description	Category	Subcategory
Type A	HE associated with acute liver failure	Not applicable	Not applicable
Type B	HE associated with portosystemic bypass and no intrinsic hepatocellular disease	Episodic	Precipitated (provocative factors exist) Spontaneous (no provocative factors) Recurrent
Type C	HE associated with liver cirrhosis and portal hypertension or portosystemic shunts	Persistent	Mild Severe
		Minimal	Not applicable

neurophysiological tests reveal abnormalities in cognition and psychomotor functions. That is why in 2011 an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus proposed to upgrade West Haven's criteria by introducing new terms in HE classification: ''covert HE'' and ''overt HE'' [3]. The overt HE was classified into 3 stages according to severity of mental state impairment, while covert HE represents HE grade 1 and MHE. Patients without HE are considered as unimpaired according to this classification [3].

MHE is defined as cognitive impairment in patients with liver disease (with or without portosystemic shunts), or in patients with portosystemic shunts without liver disease. MHE diagnosis is not based on patient anamnesis or what his relatives told or objective neurological assessment, but only on neuropsychometric or neurophysiologic tests, when there is no other known cause which may negatively influence cognitive assessment results. It is recommended to apply MHE definition not only for patients with hepatic cirrhosis (C type HE) as it was approved in Vienna, 1998, but also if other type of portal hypertension exists (B type HE) [10].

MHE is rarely cared for in everyday practice; only patients with clinically remarkable HE are treated. Therefore in this article we will pay particular attention to MHE, which impairs patient and his/her care giver's everyday activities and decreases their quality of life.

2. MHE relevance

The true frequency of MHE is unknown. For its diagnosis, neuropsychologic, neurophysiologic tests (electroencephalography, P300 evoked potentials), computerized tests (critical flicker frequency test, inhibitory control test) or their combinations are used [11–15]. Evaluation criteria and normative vary in different studies and therefore the observed MHE rate ranges from 22% to 74% in cirrhotic patients [11,16–27]. When psychometric tests are used, attention is not always paid to patient's education and age. Also often performed for the assessment of low grade of HE paper–pencil tests were evaluated as having high rate of errors and are mostly suitable for the following up of clinical improvement in individual patient than for the classification of patients into groups of MHE or overt HE [28]. Recently introduced critical flicker frequency analysis (CFF) objectively and reproducibly reflects HE severity and helps reliably separate cirrhotic patients with and without HE, however its results slightly depend on age, education and training [2,14,28–31]. Moreover, there is not clear whether abnormal CFF values reflect disturbances of quality of life and whether CFF threshold analyses are suitable for the follow-up of patients during treatment and in clinical trials [32].

There are several studies described rate of HE after transjugular intrahepatic portosystemic shunt (TIPS) procedure, but there are no epidemiological data yet about MHE prevalence after this procedure [33]. Data from trials showed the risk factors of MHE development including the degree of liver damage [11,16–21], esophageal varicose [18], previous portosystemic shunts operation, patient's age [11,17,20], and clinically significant HE episodes in anamnesis [18]. It is interesting, though, that the etiology of liver disease does not have a major influence [17,19,20,22].

During recent decades, many of clinical studies have been conducted proving negative influence of MHE on quality of life, safety and on driving fitness of patients. One of such studies on quality of life was conducted by Groeneweg et al. Sickness impact profile was measured and assessed that the social connections are mostly impaired, also emotions and its expression change, and mobility, housekeeping, sleep and awakening regime, leisure time and recreational activities are all disturbed [34].

MHE impairs attention, alertness, orientation and learning processes. According to recent studies results, patients with MHE have higher risk of car accidents, impairment in attention affects an individual's ability to react to unexpected traffic conditions [23–27].

MHE is not lethal and also no hospitalization is needed, though it is undoubtedly a burden for both patient and health institutions. Blue-collar workers suffer more than white-collar workers. Half of the patients with MHE have no permanent job compared to 15% of patients without impaired cognitive functions [18]. Because of the state of their health, blue-collar workers lose up to 60% of workplaces, and white-collar workers, up to 20% [35].

3. HE pathogenesis

Most researchers agree that independently on HE type (A, B or C), different degrees of cerebral edema occur. The molecular processes and all possible mechanisms important for HE development are under research.

3.1. *Role of ammonia in HE development*

The pathogenesis of HE is complicated and polyetiological. It is considered that ammonia plays a key role in this [36]. Ammonia is a neurotoxin, which impairs transport of amino acids, water, and electrolytes through membrane of neurons and astrocytes, disturbs metabolism of amino acids, energy consumption in brain, and nerve potentials transmission through synapses. Over time, ammonia even causes morphological changes of astrocytes and ''Alzheimer type II'' astrocytes occur.

Ammonia is produced in the digestive tract of humans when intestinal bacteria disintegrate amines, amino acids, purines, and urea. Glutaminase catalyzes the deamination of glutamine to form glutamate and ammonia in enterocytes.

The main transformation of ammonia proceeds in liver. Ammonia turns into urea through Krebs cycle, and glutamate with help of glutamine synthetase becomes glutamine. In case of liver cirrhosis, because of both – decrease of liver function capability and portosystemic shunts – the concentration of ammonia in circulation increases. The reserve mechanisms of detoxification of ammonia in skeletal muscles, kidneys and brain turn on.

In human's skeletal muscles the enzyme glutamine synthetase presents. It is not very active in normal case. Though, it helps to neutralize excessive ammonia in case of liver cirrhosis. Regrettably, it is common that muscles of

patients with progressive liver cirrhosis becoming atrophic and this path of ammonia detoxification fails with time also. Another important organ of ammonia detoxification is kidneys. They produce not only glutamine synthetase, but also a glutaminase [37].

In case of hyperammonemia brain also participates in conversion of ammonia. The only cells in the CNS capable of ammonia detoxification are astrocytes [38]. High amount of glutamate in astrocytes glutamine synthetase transforms into glutamine that causes the osmotic disbalance in the cell. The amount of intracellular water increases, and edema of astrocytes occurs. Glutamine is transported to neurons where it is deaminated into glutamate by glutaminase. Glutamate stimulates postsynaptic receptors of neurons. That is why patients with A type HE are anxious, agitated, have even convulsions, coma, and intracranial hypertension may occur. Because of chronic hyperammonemia the mechanisms to keep homeostasis turn on. Osmolytes such as myo-isonitol and taurine are released from astrocytes [39], and development of edema of astrocytes is slowed down. The amount of glutamate receptors in postsynaptic membrane decreases, carriers of glutamate are inhibited, and less of glutamate returns back into astrocytes [40]. High amount of glutamate accumulates in the postsynaptic space and suppression of glutamate receptors occurs. That is why patients with C type HE are more commonly slower, sleepy, etc.

Ammonia undoubtedly is important in pathogenesis of HE, though no significant correlation between concentration of ammonia in arterial blood and severity of HE was observed. Zieve et al. [41] were the first who raised the hypothesis that few toxins having synergic effect with ammonia are important for HE development.

3.2. GABA theory

GABA (gamma amino butyric acid) is neuroinhibitor produced in the gastrointestinal tract. About 24%–45% of neurons have GABA receptors. GABA receptors complex links not only GABA, but also has binding sites of benzodiazepines and barbiturates. For a long time was thought, that in case of liver cirrhosis the concentrations of GABA and benzodiazepines increase in blood and induce HE. Also there was the hypothesis, that GABA receptors of neurons become more sensitive, though these theories were recently denied [42]. Another study prompts to highlight a role of the TGR5 receptor in the increasing of GABA-nergic tone in patients with HE [43]. According to this study TGR5 are expressed in astrocytes and neurons. Through elevation of cAMP TGR5 may promote a rise in intracellular calcium concentrations which in turn regulate neurotransmitter release from astrocytes and neurons and provoke production of reactive nitrogen and oxygen species (RNOS/ROS) [43]. Ongoing intensive research will provide us with more circumstantial understanding of neurosteroids role in development of HE.

3.3. The role of neurosteroids

Neurosteroids (NS) in brain are produced by both glial cells and neurons. The main place of neurosteroids synthesis is mitochondrial endoplasmic reticulum of astrocytes [44]. Neurosteroids are partial agonists of GABA receptors, which increase GABA-nergic tonicity by connecting to these receptors and have influence on development of HE. Their synthesis is stimulated by activation of peripheral-type benzodiazepines receptors (PTBR), which are localized in mitochondrial membranes of astrocytes. In case of liver cirrhosis, manganese and ammonia concentrations in brain increase and stimulate these receptors. PTBR regulates transportation of cholesterol and NS synthesis. Also findings from autopsy materials of patients who died from hepatic coma [45–47] and in vivo research of patients with MHE [48] have shown much higher expression of PTBR. Presumably, PBTR may be synthesized also by microglia (CNS macrophages) under infection conditions.

3.4. Inflammation and HE

In the past decade more evidence was found about inflammation process and its importance for HE development. The brain cells (astrocytes and microglia) are capable to synthesize proinflammatory cytokines (TNFα, IL-6, IL-1) as a response to inflammatory process in human body [46]. Those cytokines increase blood–brain barrier permeability for ammonia and its passage into astrocytes [49–51]. They also take a part in the cellular and molecular mechanisms of learning, memory and cognitive processes. IL-6, IL-1, and TNF are reckoned to be important for plasticity of synapses, long-term potentiation, neurogenesis, and consolidation of memory. Variations of their concentration disturb these processes [52].

Shawcross et al. conducted the trial of cirrhotic patients treated for systemic inflammatory response syndrome [53]. Amino acid preparations per os were administered for them with purpose to increase the concentration of ammonia in the blood. When infection was successfully treated and inflammatory cytokines (IL-6, IL-1β, TNFα) decreased to normal levels, patients performed psychometric tests better than before the treatment, though hyperammonemia was still artificially maintained [54]. In another study 84 patients with liver cirrhosis participated. White blood cells count CRP, ammonia, nitrates/nitrites, IL-6, and amino acids before and after amino acids solutions intake or placebo were assessed.

MHE did not depend on ammonia concentration in blood or degree of liver damage. However, higher inflammatory indices in the blood of patients with MHE were found vs patients without MHE. It was also found that hyperammonemia significantly influenced deterioration of neuropsychological functions of patients with higher rates of inflammatory indices [55].

3.5. Oxidative stress

In experimental trials on animal models was found that ammonia, inflammatory cytokines, hyponatremia, and benzodiazepines activate synthesis of reactive nitrogen and oxygen products [56,57]. N-methyl D-aspartate (NMDA) receptors are important for the production of free radicals. Their activation decreases the activity of antioxidative enzymes (glutathione peroxidase, catalase, superoxide dismutase) and causes oxidative stress. The oxidative stress is avoided by administering of NMDA receptors antagonists [58,59].

Acute astrocytes edema may be triggered by reactive nitrogen and oxygen products in vitro [60]. It is still controversial "what comes first": astrocytes edema which caused stimulation of NMDA receptors or oxidative stress which caused changes of astrocytes.

Other action of reactive oxygen products is tyrosine nitration which impacts transport of substrates in astrocytes, permeability of blood–brain barrier, and astrocytes and brain edema occurs [32]. Influence of hyperammonemia induced oxidative effect on synthesis of RNA and proteins, which are necessary for studying and memory, is under research [61,62].

3.6. *Manganese*

Manganese is a neurotoxin, which accumulates exceptionally only in basal ganglia of brain. Its accumulation may be seen on MRI scan. Manganese vanishes when the functions of liver regenerate [63,64]. Presumably, this is a heavy metal that causes formation of Alzheimer's II astrocytes. It also stimulates PBTR and increases synthesis of neurosteroids, and GABA-nergic tonicity in brain [65].

3.7. *MHE and intestinal microflora*

Not only hyperammonemia and inflammation are important for the development of MHE, but also changes of composition of intestinal bacteria (proportion between ammonia producing and not producing bacteria). After comparison of microflora of patients with MHE and healthy subjects the higher amount of aerobes (*Enterobacter*, *Enterococcus*) and anaerobes (*Clostridium*) and lower amount of *Bifidobacterium* were found in the first group. The direct correlation between intestinal bacteria and degree of liver functions insufficiency was observed [66].

During other study the bacteria excess syndrome was investigated in cirrhotic patients with and without MHE. This syndrome was detected more often in patients with MHE (38.6% vs. 8.9%). The bacteria excess syndrome also was observed more often in Child-Turcotte-Pugh B and C classes than in A class. A longer intestinal transit time was also detected for patients with this syndrome ($P < 0.0001$) [65,66].

4. Concluding remarks

That is still complicated to distinguish unimpaired patients and those with minimal and grade 1 hepatic encephalopathy because of lack of objective diagnostic tools.

Taking into consideration recent knowledge of HE pathogenic mechanisms some clinical recommendations can be formulated. Dietary treatment should be recommended in addition to drug therapy for appropriate maintaining of normal nutritional status and muscle mass. Consumption of food with higher amounts of branched amino acids and less aromatic amino acids can be helpful for the reducing of ammonia production and absorption. Also benzodiazepines and barbiturates should be avoided for patients with HE. Other treatment strategies such as reducing of ammonia production (lactulose, probiotics, and antibiotics) and inducing of ammonia detoxification (L-ornithine L-aspartate) must be used.

Further clinical studies are needed to elucidate more precisely the impact of all mentioned neurophysiological impairments pathways which cause hepatic encephalopathy as well as novel HE treatment regimens.

Conflict of interest

The authors state no conflict of interest.

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