CURRENT CONCEPTS IN MINIMAL HEPATIC ENCEPHALOPATHY

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CURRENT CONCEPTS IN MINIMAL HEPATIC ENCEPHALOPATHY (Abstract): Minimal hepatic encephalopathy (MHE) defines the presence of neurocognitive impairments in patients with cirrhosis or portal-systemic shunting that show a normal neurologic and psychiatric status on clinical examination. Although ammonia has the central role in MHE pathogenesis, factors such as infection, oxidative stress, manganese or intestinal bacterial overgrowth contribute to the development of the neurocognitive deficits associated with this disease. Many methods have proven useful in identifying MHE but because of the major drawbacks (standardization requirements, high price, sophisticated equipment, and limited access) a gold-standard test is still missing. Although beneficial, the treatment of MHE is not routinely recommended and should be taken into consideration in patients at risk for accidents and in those with cognitive complaints or decline in work performance. **Keywords:** MINIMAL HEPATIC ENCEPHALOPATHY, LIVER CIRRHOSIS

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver failure and/or portosystemic shunts (PSS). The clinical picture of HE includes neuropsychiatric abnormalities, which may vary from subclinical manifestations to coma (1). Factors such as multifactorial etiology, polymorphism of clinical manifestations, oscillating evolution, and the wide variety of precipitating factors constituted prerequisites for developing a guideline for classification, diagnosis and treatment of this pathology. The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver established a working group that put forward guidelines regarding the nomenclature used for defining and systematizing HE based on clinical manifestations (fig 1).

The current standardization individualizes Minimal Hepatic Encephalopathy (MHE) as a separate entity together with the old West Heaven criteria. According to the nomenclature used by the International Society for the Study of Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN), MHE and grade I HE are included into covert HE (1, 2). MHE is defined by neurologic and psychiatric status within normal limits during clinical examination, but with neurocognitive deficits detectable by psychometric or neuropsychological testing (3). Neurocognitive abnormalities include impaired attention, deficits in fine motor skills, disorders of the visual-spatial perception and altered executive functions (4, 5).
PATHOGENIC THEORIES

The mechanisms involved in MHE pathogenesis are not fully understood, but even in 2014 ammonia continues to play the central role. Recent studies have pointed to the importance of additional factors, such as inflammation, oxidative stress and intestinal bacterial overgrowth, in generating neuropsychiatric abnormalities in this category of patients (6).

Ammonia has a decisive role in the pathogenesis of MHE. Physiologically, ammonia is converted to urea in the liver. This metabolite is water-soluble and it is excreted from the body by the kidneys through urine. In patients with chronic liver diseases or portosystemic shunts, this metabolic pathway is compromised and ammonia degradation occurs primarily in muscle cells, and in the cells of the central nervous system. The extrahepatic catabolic process makes use of the amino-glutamic acid to transform ammonia into glutamine (7, 8). MHE is a form of gliopathy caused by type II astrocytes, the only cells at brain level containing glutamine-synthetase that can...
metabolize ammonia. The intracellular glutamine concentration within astrocytes increases proportionally with the level of ammonia in the blood. An active osmolyte, glutamine draws water inside the astrocytes, determining their increase in volume, while causing the secondary development of brain edema and intracranial hypertension (9, 10). This theory is supported in a study by Tanigami et al. performed on animal models, which revealed the lack of astrocyte volume expansion following the administration of methionine-sulfoximine (glutamine-synthetase inhibitor) (11).

Secondary to prolonged exposure to high ammonia concentrations, astrocytes undergo morphological and functional changes. During this stage, brain cells undergo a transformation process turning into type II Alzheimer astrocytes, characterized by large nuclei, prominent nucleoli and chromatin marginal arrangement (12). In order to compensate for the increase in volume, the astrocytes release osmotic-active molecules, such as myo-inositol and taurine (13, 14). According to a study by Shawcross et al. (15), the low levels of intracellular myo-inositol are associated with increased risk of neurological impairment. Glutamate transporters situated along the astrocyte membrane are inactivated and the activity of post-synaptic receptors for glutamate is inhibited. These functional transformations determine alterations of the neuronal function, reducing the conduction of nervous impulses (16, 17). Ammonia alters the function of the hematoencephalic membrane and determines the decrease of small and medium chain amino-acids and an increase in the inflow of neutral long-chain and aromatic amino-acids. Secondarily, the intracerebral synthesis of catecholamines (serotonin and dopamine) is reduced, with inhibitory effects on neurotransmission (18, 19).

Infection and inflammation. Although ammonia is an important factor in MHE pathogenesis, 10% of HE patients have normal levels of ammonia in the blood (20). Except for ammonia, there are other neurotoxic compounds derived from the bacterial metabolism showing high serum levels in patients with chronic liver diseases: phenols and mercaptans. Produced by bacteria in the bowel, these substances are not catabolized in the liver due to the impaired liver function and they are transported to the brain, where they exert their neurotoxic effect (21). A recent study by Bajaj et al. emphasizes the important role of acute bacterial infections and associated inflammation in the development of neuro-psychiatric anomalies in patients with HE. The authors identified imbalances in the intestinal microbiome of cirrhotic patients. The presence of certain bacterial families (Alcaligenecae, Porphyromonadaceae, Enterobacteriaceae) in the stool of patients with overt hepatic encephalopathy (OHE) was associated with systemic inflammation and the presence of cognitive deficits (22). Moreover, inflammation and inflammatory mediators enhance the negative effects that ammonia has on the central nervous system (23). Studies on astrocytes by Alvarez et al. and Rama Rao et al. demonstrated an increase in mitochondrial permeability under the influence of ammonia, TNF-α, IL-6, IL-1β and IFN-γ. High levels of IL-6 and TNF-α proinflammatory cytokines were found in the blood of patients with MHE (24, 25).

Oxidative stress. Molecular studies on rats revealed a rise in the synthesis of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by the astrocytes.
following exposure to ammonia, pro-inflammatory cytokines or benzodiazepines (26, 27, 28). On the other hand, Reinehr et al. revealed an increase in astrocyte volume when exposed to ROS and RNS (29). According to the hypothesis of Albrecht and Norenberg, glutamine determines an enhancement of the oxidation processes in the astrocytes through intra-mitochondrial release of ammonia. It later favors the creation of ROS and RNS through calcium-dependent reactions. Moreover, ROS mediates tyrosine nitration reactions. Tyrosine nitrate alters the permeability of the hematencephalic membrane, favoring the expansion of the astrocyte volume and cerebral edema (30).

Manganese is a neurotoxin that accumulates in the central nervous system (CNS) preferentially in the basal ganglia and may be pointed out by magnetic resonance imaging (MRI) (31). In a MRI study on cirrhotic patients with portacaval anastomoses or transjugular intrahepatic portosystemic shunt (TIPS), Spahr et al. revealed a hyper-signal at basal ganglia level in 88% of the patients. Additionally, 89% of the patients presented extrapyramidal symptoms and 67% of patients had increased levels of manganese in the blood. These findings are reversible after the normalization of liver function (32,33). Manganese homeostasis alterations may contribute to the development of cognitive deficits present in the clinical picture of patients with liver cirrhosis (31, 32, 33).

Neuromodulators. Ammonia and manganese determine increase in the density of peripheral type benzodiazepine receptors (PBR) in the brain. These receptors regulate the synthesis of neurosteroid hormones like tetrahydro-progesterone (THP) or tetra-hydroxycorticosterone (THDOC) by the astrocytes and are present in high numbers in the CNS of patients with MHE. THP and THDOC potentiate the activity of gamma-aminobutyric acid (GABA) receptors, with inhibitory effect on the nerve conduction in the CNS (34, 35). This theory might explain the impairment of fine motor skills and coordination or the psychomotor disorders seen in patients with MHE (36, 37).

Intestinal bacterial overgrowth (IBO). A study on patients with MHE by Liu et al. revealed changes in the intestinal microbiome with an increase in the number of urease producing bacteria. Therapeutic intervention (synbiotic treatment) was associated with improvement of bowel flora imbalances, as well as better psychometric tests results. (38). In another study, Gupta et al. revealed a high prevalence of IBO in patients with MHE (38.6%) (39).

**CLINICAL AND SOCIOECONOMIC IMPLICATIONS**

MHE has a negative effect on the quality of life and determines alterations of the psychomotor skills and the ability to process information (40, 41). Prasad et al. revealed the impairment of daily activities such as social interaction, emotional behavior, reading, alertness and recreation periods in patients with MHE (42). Moreover, sleep disorders constitute a frequently met feature associated with chronic daytime fatigue and circadian rhythm disorders (43, 44). Weissenborn et al. outlined the negative impact that MHE exerts over short-term memory. Memory disorders have also been associated with attention and visual perception deficits (45).

Particular aspects of cognitive deficits in MHE determine differences in the ability to work in various professions. Cirrhotic patients involved in professions that require
constant vigilance and coordination (e.g. operators of industrial machinery or drivers) are more severely affected by MHE compared with the patients dealing with predominantly intellectual or verbal tasks (e.g. administrative or executive functions) (46). MHE may adversely impact the socioeconomic status of patients by reducing workplace performance. Approximately half the patients diagnosed with MHE do not have a job (47). The decrease in workplace performance and the diminution or the absence of a salary involves substantial moral and material losses for the individual (46). MHE affects both the individual and the society, generating high costs through repeated hospitalizations and treatment, in the evolution towards OHE development (48). Besides affecting the quality of life, MHE patients have an increased risk of progression to OHE. The patients constitute a potential danger both to themselves and to the wider community (49). Attention deficits, memory alterations and persistent fatigue associated with MHE contribute to impairment of driving abilities and an increased number of driving errors (exceeding the permissible speed, illegal turns, or accidents) (50, 51, 52).

Although MHE represents the initial stage of the neurocognitive impairment spectrum associated to cirrhosis, some studies correlate it with increased mortality (53). In a study by Dhiman et al., MHE patients showed faster progress towards grade I HE or OHE, and an increased rate of progression to liver failure. In addition, the study showed higher mortality rates in patients with MHE as compared to those without MHE (39.1% vs. 22.9%). (54)

**DIAGNOSIS**

MHE diagnosis requires the use of neuropsychological and/or neurophysiological tests in order to document neurocognitive alterations occurring in patients with chronic liver diseases or PSS. Standard clinical examination does not reveal any neurological anomalies or mental disorders. In what follows, we will point out MHE diagnosis criteria adapted from Simon-Talero et al.: diagnosis of a disease that can cause MHE - cirrhosis, PSS or portal vein thrombosis; normal neuropsychiatric status on clinical examination; absence of grade I HE or OHE; documentation of neurological alterations by formal neuropsychological assessment, neuropsychological tests, computerized tests or neurophysiological tests; the exclusion of other factors or diseases that can cause neurological impairment - metabolic, cerebrovascular, neurodegenerative diseases, alcoholism, vision impairment etc. (55).

The tests used for MHE diagnosis assess multiple cognitive areas including: working memory, inhibitory control, psychomotor speed, reaction speed and visual-motor coordination. We list below the techniques used for MHE diagnosis adapted from Dhiman et al.: Neuropsychological assessment using series of tests with proven clinical applicability, although time-consuming. Computerized tests (Critical Flicker Frequency, Inhibitory Control Test, Continuous Reaction Times) are rapid, easily applicable tests but with limited data regarding diagnostic significance and requiring standardization prior to use. Neurophysiological tests (Electroencephalography, Spectral Electroencephalography, Evoked Potentials P300) are objective, may be repeated but require sophisticated equipment in order to be applied. Short neuropsychological tests (PHES) have high sensitivity, demonstrated clinical applica-
bility with quick results but also have limited access and requirements of standardization prior to use. CDR computerized assessment battery are sensitive with rapid results but the limited access, high price and the need for training courses prior to use constitute major drawbacks for widespread usage (56). ISHEN recommends psychometric tests such as PHES, as a first-line option for the diagnosis of MHE. In the absence of prior PHES standardization, previously studied alternative tests will be used, for which normative data is available (57).

At present there is no universal test for the diagnosis of MHE, and there are controversies in the literature regarding the benefits resulting from the treatment of this pathology. Screening all cirrhotic patients for MHE is not recommended. The neuropsychological assessment should be individualized and taken into consideration especially in patients with an increased risk of accidents (labor or machine) and in those with cognitive complaints or associating alteration of the work capacity (55).

**TREATMENT**

Given the central role ammonia has in MHE pathogenesis, literature studies focused on investigating pharmacological agents that decrease ammonia levels. The therapies are similar to those used for the treatment of OHE: non-absorbable disaccharides (lactulose), antibiotics (rifaximin), probiotics/synbiotics and branched amino-acids (58). In clinical setting, non-absorbable disaccharides are most commonly used for the treatment of MHE (58). However, a meta-analysis of randomized trials suggests that antibiotics such as rifaximin may prove more useful (59). Recent studies have shown the benefits of lactulose and rifaximin in improving the cognitive function and the quality of life in cirrhotic patients with MHE. (60, 61, 62, 63) Given their modulating properties of the intestinal microbiome, probiotics, synbiotics and yoghurts may stand as effective, reliable and long-term solutions for the treatment of MHE. Studies to date are inconclusive because they were conducted over short periods of time and on a relatively small number of patients (64, 65).

MHE medical treatment should be individualized and requires a dynamic evaluation following objective indicators for an accurate assessment of the therapy response. Treatment is mainly targeted at patients with cognitive complaints, those associating alteration of the work capacity and drivers. (55)

**CONCLUSIONS**

MHE is the initial stage of the spectrum of neurocognitive impairment associated with liver cirrhosis. Despite the term "minimal", this entity is associated with reduced quality of life, socioeconomic status deterioration, reduced driving ability and faster progression to OHE.

Ammonia has a central role in MHE pathogenesis. Complementary factors such as inflammation, oxidative stress, manganese and IBO require further studies in order to determine the exact extent of their involvement in the development of MHE. Although not routinely recommended, early diagnosis and treatment in patients with MHE leads to an improvement of the cognitive deficits and increased quality of life.

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