Review article

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RECENT THEORIES OF PATHOGENESIS OF HEPATIC ENCEPHALOPATHY IN HEPATITIS C VIRAL INFECTION

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Hepatic encephalopathy is potentially reversible, or progressive neuropsychiatric syndrome characterized by changes in cognitive function, behavior and personality changes, and transient neurologic symptoms and characteristic electroencephalographic patterns associated with acute and chronic liver failure. For some time, there has been controversy regarding the origin of toxins responsible for the change of mental state. It was found that the occurrence of hepatic encephalopathy is responsible for multiple organ peripheral changes (intestinal changes, abnormalities of portal-systemic circulation, liver failure, loss of muscle tissue), changes in brain intracellular communication (osmotic changes, astrocytes and axonal abnormalities in communication, changes in cerebral perfusion) and ammonia, endogenous benzodiazepines, gamma amino butyric acid, derivatives of methionine and false neurotransmitters. The aforementioned metabolic factors that contribute to the development of hepatic encephalopathy are not mutually exclusive and multiple factors may be present at the same time. *Acta Medica Medianae 2013;52(2):51-55.*

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Introduction

Hepatic encephalopathy (HE) is a potentially reversible, or progressive neuropsychiatric syndrome characterized by changes in cognitive function, behavior and personality changes, and transient neurologic symptoms and characteristic electro-encephalographic patterns associated with acute and chronic liver failure (1, 2).

Hepatic encephalopathy is a complication of cirrhosis, which is often viewed as part of severe liver failure. Characteristically, it occurs during development of acute encephalopathy with the slump awareness, manifesting as confusion or coma. Precipitating factor can often be identified. Treatment of this episode is directed to the correction of precipitating factor. Once the precipitating condition is resolved, encephalopathy also disappears, and the patient recovers to its previous state. However, in patients with low reserves of hepatic function, HE can become a chronic condition. Low reserve predisposes patients to spontaneous development of HE. Usually, there is a precipitating factor, so during the diagnosis and treatment, these aspects should be considered (3, 4).

Acute HE is a disorder that often follows a fulminant hepatitis i.e. fulminant hepatic failure. It occurs most commonly during the first two to eight weeks from the onset of the disease (primarily referring to the signs of icterus, and other symptoms). By definition, fulminant hepatitis is always accompanied by HE (5).

Chronic encephalopathy can be manifested as frequent episodes of acute encephalopathy (chronic recurrent encephalopathy) or permanent neurological manifestations (chronic persistent encephalopathy). Distinguishing between these two forms is rather subjective and reflects in emphasizing neurological manifestations (6).

The pathogenesis of hepatic encephalopathy

For some time, there has been controversy regarding the origin of toxins responsible for the change of mental state. It is now certain that there are peripheral multiorgan changes, and changes in brain intracellular communication, due to changes in astrocytes. There has been debate about the role of ammonia, synergistic toxins, gamma aminobutyric acid (GABA) and endogenous benzodiazepines in the development of HE (4).

Peripheral changes

A. Intestinal

There is controversy regarding the participation of Helicobacter pylori, which produces ammonia in the stomach, in the pathogenesis of hepatic encephalopathy. Some studies have shown a high prevalence of infection in patients with HE in alcoholic hepatitis, and in those with cirrhosis or chronic encephalopathy. However, eradication of H. pylori does not interfere with the levels of ammonia in this group of patients, and contribution to the development of HE is therefore minimal (7, 8).

B. Portal-systemic communication

It is shown that some congenital abnormalities that cause portal-systemic shunts are manifested in children by episodes of HE, even without pre-existing liver disease. Also, patients with cirrhosis and portal-systemic encephalopathy develop shunts easier than patients without shunts (2).

C. Liver failure

Many studies argue that the failure of the liver is the main cause of HE, resulting from the reduced functional capacity, which reduces the detoxification of ammonia, which leads to increasing its level in plasma and the resulting clinical manifestations of these patients' functions. Degree of CNS damage correlates with the degree of liver damage (9).

D. Muscle tissue

Decreased muscle mass in cirrhotic patients may be a predisposition for the development of HE. Muscle loss cannot be explained only by the presence of liver disease and nutritional status of the patient, but also by increased levels of some cytokines such as tumor necrosis factor alpha (TNF-α), which activates the transcription factors NK-like, that further results in decreased synthesis of myosin. Consumption of muscle is associated with lower metabolic capacity of detoxification of ammonia and glutamine, and the formation of HE (10, 11).

Brain changes

A. Osmotic changes

Some studies have shown that there are osmotic changes in patients with brain edema and liver dysfunction. On the one hand, brain edema develops increasing intracerebral pressure and can lead to incarceration and death (9). Glutamine produced for detoxification of ammonia in astrocytes is considered osmolar organic substance which can produce edema in astrocytes. It has been noted that a water channel aquaphorin-4 introduces water into the cell. There is evidence that the brain adapts to changes in chronic liver disease. Direct and indirect deterination of organic osmolars by reviewing resonance spectroscopy in humans showed a loss of mioinositol, taurine, and glyceryl-phosphocholin which are osmolars used by astrocytes in the regulation of intracellular osmolarity (3, 12, 13).

B. Axonal communication

There is also evidence of the essential role of astrocytes in maintaining normal function of neurons. Alzheimer type 2 cells (astrocytes) may show some abnormalities: reduced activity of the neurotransmitter (glutamate), increased expression of benzodiazepine receptors and increased activity of monoamine oxidase (MAO). As a result, there are changes in metabolic communication between astrocyts and other cells. For example, astrocytes synthesize neurosteroids that activate GABA receptors and endogenous benzodiazepine receptors. The brain does not create cycles of urea and ammonia is removed by glutamine synthetase in the reaction of ammonia with glutamate producing glutamine. With excess ammonia, logically, there is an excess of glutamine (3, 13).

C. Brain blood flow and endothelial communication with astrocytes

Patients with HE have fluctuations in cerebral perfusion. Some experimental models have shown increased cerebral perfusion in the presence of high levels of ammonia. There can be activated signals generated after the intracerebral glutamine synthesis in astrocyts. Hypothermia and cerebral edema play an important role in the development of low cerebral perfusion. Cirrhotic patients have decreased blood flow to the brain, probably due to peripheral vasodilatation. These changes may be the cause of decreased metabolic activity (3, 13).

D. Other hypotheses:

- Ammonia

Ammonia is a basic element in the pathogenesis of HE. Following the detoxification of ammonia by astrocytes, some neurochemical changes occur. There are many factors that interact with ammonia, including changes in astrocytes (hyponatremia, elevated cytokines, changes in ligand astrocytes), and produce anatomically and neurochemically substrate synergism which increases the possibility for the occurrence of HE. However, ammonia levels do not correlate with the severity of encephalopathy. The level of glutamine and alpha-ketoglutarate in cerebrospinal fluid correlate with the degree of HE. Basic mechanisms of action of ammonia are as follows: direct effect - the cell membrane of neurons (inhibition of Na^+ and K^+ ATP-ase) or postsynaptic inhibition (blocking chloride pump) and an indirect effect – disruption of glutamatic neurotransmission impairs the function of neurons (glutamate is the major excitatory neurotransmitter) (14).

The main source of ammonia is the intestinal tract. It is created under the action of bacterial proteases, urease and amino oxidase to the intestinal contents, and by hydrolysis of glutamine. Under normal circumstances, most of the ammonia enters the port bloodstream to the liver portal tracts, metabolized in hepatocytes, and it remains a bit in the systemic circulation. However, when the majority of hepatocytes are destroyed or dysfunctional (fulminant hepatitis and other liver diseases), ammonia from the intestine passes through the liver non-meta-

bolized, and passes through the systemic circulation to the CNS (14).

Turbidity neurotransmission in elevated concentration of ammonia is associated with a decrease. Ammonia intoxication leads to hyperkinetic preconvulsive state, which does not correspond to HE and increases neural inhibition rather than excitation (14).

- Endogenous benzodiazepines and GABA

The role of these substances in the GABA-mediated change (GABA-ergic neurotransmission) is not well understood. Some studies on flumazenil did not yield significant results; also, ammonia may activate the GABA-ergic pathways in the synthesis of neurosteroids astrocyts, as already mentioned (10).

Gamma-aminobutyric acid is the major inhibitor of neurotransmission. It is synthesized from glutamate by glutamate dehydrogenase in presynaptic neurons and reversed in vesicles. Release of GABA neurons synapse cracks is associated with the specific GABA receptors in the postsynaptic membrane. This receptor is also part of a larger receptor complex, important for the binding of benzodiazepines and barbiturates. By binding of either GABA or benzodiazepine a channel for chloride opens, and their influx hyperstimulates the postsynaptic membrane and neuroinhibition occurs. Thus, the increase in GABA-mediated neurotransmission, followed by a decrease in motor function and consciousness, are the two cardinal manifestations of HE (10).

Gamma-aminobutyric acid is synthesized by bacteria in the intestines through the portal vein and reaches the liver, where it metabolizes. In liver disease and portal-systemic shunts, GABA passes through the systemic circulation nonmetabolized. However, as is the case with ammonia, GABA levels in the serum and the degree of HE did not always correlate, even though the research focused on the aforementioned receptor complex indicate the correlation of benzodiazepines on activity in plasma and severity of HE (10).

- Derivatives of methionine

Mercaptans, derivatives of the intestinal metabolism of methionine, were thought to be caused by HE. The recent studies on metanefiol, a highly toxic mercaptan, have not indicated its involvement in the pathogenesis of HE (15).

- False neurotransmitters

Brain neurotransmission is normally carried out by means of dopamine and catecholamines, and may be inhibited by amines. These amines are produced by the effect of the bacteria from the column or by altered cerebral metabolism precursors (15).

Decline in the level of branched-chain amino acids (valine, leucine, isoleucine; drop occurs due to increase in their metabolism outside the liver) may favor the entry of aromatic amino acids (tyrosine, phenylalanine, tryptophan, resulting in impaired liver dissemination) in the brain, which are precursors of false neurotransmitters, which render the waste unrecognizable synthesis of glutamine. Aromatic amino acids easily undergo a modified blood-brain barrier in the altered balance of their concentration. The increase in levels of phenylalanine in the brain inhibits the production of dopamine, and the creation of false neurotransmitters such as octopamine and phenylethanolamine. Clinical experience with the branched-chain amino acids is of great importance because it is possible that amino acids have a direct effect in the muscles, increasing the detoxification of ammonia. Other routes of transmission may be involved in the HE: serotonin (5-hydroxitryptamin, 5-HT), opioids and catecholamines. Serotonin is represented in the control of cortical wake cycles and sleep / wakefulness, and the general state of mind. Serotonin is formed from tryptophan, a precursor tryptophan is an aromatic amino acid whose level increases in plasma, CSF and brain of patients with HE, and there is a possibility of increased synthesis of serotonin in HE (7).

Other additional factors that favor the occurrence of recurrent episodes of HE are the nutritional status, particularly in alcoholics, who have a deficiency of vitamins and micronutrients. One such example is zinc deficiency, which is a cofactor in the urea cycle. Zinc supplementation, using a dose of 600 mg per day, is considered in the encephalopathy but showed no additional benefit. However, it seems reasonable to measure plasma levels of zinc and zinc supplements added when levels are low. The issue of colonization of the stomach with H. pylori, an organism that produces urease, has been recently discussed. Eradication of H. pylori may be useful in other diseases, but not associated with lower levels of ammonia or improvement in HE (7). Hepatic encephalopathy is the result of a combination of hepatic dysfunction (hepatic insufficiency), accumulation of toxins and the establishment of portal-systemic shunt. The main precipitating factor (that is not a specific cause) has changed the level of plasmatic ammonia. Pathogenetic mechanism involves the production of false neurotransmitters, facilitated sensitivity of neurons by gamma aminobutyric acid (GABA), increased plasma levels of endogenous benzodiazepines, decreased activity of enzymes of urea cycle as a consequence of zinc deficiency, and finally, deposition of manganese in the basal ganglia (15).

If the cause of fulminant hepatitis is HE, then all its associated conditions and complications (cerebral edema, coagulopathy, hypoglycemia, electrolyte and acid-base disorders, renal failure, hemodynamic changes, respiratory complications, acute pancreatitis, infection) are important factors in the development of HE (15, 16).

Conclusion

The aforementioned metabolic factors that contribute to the development of hepatic encephalopathy are not mutually exclusive and multiple factors may exist at the same time.

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NOVIJE TEORIJE PATOGENEZE HEPATIČNE ENCEFALOPATIJE KOD VIRUSNE INFEKCIJE IZAZVANE HEPATITISOM C

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Hepatička encefalopatija je potencijalno reverzibilan ili progresivan, neuropsihijatrijski sindrom okarakterisan promenama u kognitivnoj funkciji, izmeni ponašanja i ličnosti, kao i prolaznim neurološkim simptomima i karakterističnim elektroencefalografskim šemama, udruženim sa akutnom i hroničnom insuficijencijom jetre. Već duže vreme postoje kontroverze u vezi sa poreklom toksina odgovornog za izmenu mentalnog stanja. Danas je utvrđeno da su za nastanak hepatičke encefalopatije odgovorne periferne multiorganske izmene (intestinalne promene, abnormalnosti portno-sistemske cirkulacije, insuficijencija jetre, gubitak mišićnog tkiva), izmene u moždanoj intracelularnoj komunikaciji (osmotske promene, abnormalnosti astrocita i aksonske komunikacije, promene moždane perfuzije), kao i amonijak, endogeni benzodiazepini, gama amino buterna kiselina, derivati metionina i lažni neurotransmiteri. Pomenuti metabolički faktori koji doprinose nastanku hepatičke encefalopatije međusobno se ne isključuju, a multipli faktori mogu postojati u isto vreme.*Acta Medica Medianae 2013;52(2):51-55.*

Ključne reči: *hepatička encefalopatija, patogeneza*

