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HYPERAMMONEMIA IN PATIENTS AT PRE-CIRRHOTIC STAGE: CLINICAL REALITY?

Abstract

Ammonia belongs to the common neuro- and cytotoxic metabolites in the human body. It is established that ammonia has hepatotoxic properties. Ammonia induces the formation of oxygen active forms, reduces the activity of endothelial NO synthase, dose-dependently decreases the cellular metabolism and proliferation of stellate cells, and promotes fibrogenesis, disturbance of intrahepatic hemodynamics and, accordingly, the formation of portal hypertension. The article describes causes of hyperammonemia in pathological conditions and physiological functions disorder. The increased level of ammonia is associated not only with various neuropsychiatric disorders in patients with liver cirrhosis, but is also shown in patients with chronic liver disease (CLD) at the pre-cirrhotic stage. The sign of minimal hepatic encephalopathy in patients with chronic hepatitis is a cognitive impairment, which manifests as a decrease in concentration, in particular when driving. The effect on hyperammonemia becomes a target for therapy in steatohepatitis of various etiologies. The use of the oral form of L-ornithine-L-aspartate effectively reduces the level of ammonia in the blood, improves cognitive function and positively affects the functional state of the liver in patients with CLD at the pre-cirrhotic stage.

Key words: *steatosis, steatohepatitis, chronic hepatitis C, hepatic encephalopathy; hyperammonemia, L-ornithine-L-aspartate*

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eNOS — endothelial nitric oxide synthase, LOLA — L-ornithine-L-aspartate, NH_3 — ammonia, NH_4^+ — ammonium ion, NO — nitric oxide, ATP — adenosine triphosphate, VEPs — visual evoked potentials, BBB — blood-brain barrier, CFF — critical flicker-fusion frequency, MHE — minimal hepatic encephalopathy, NAD — nicotinamide adenine dinucleotide, NAFLD — non-alcoholic fatty liver disease, NASH — non-alcoholic steatohepatitis, TrR — Traffic Rules, HE — hepatic encephalopathy, NCT — number connection test, CH — chronic hepatitis, CHB — chronic hepatitis B, CHC — chronic hepatitis C, CLD — chronic liver diseases, CNS — central nervous system, HC — hepatic cirrhosis

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a range of neurological or mental (cognitive or behavioral) disorders that occur in patients with hepatic insufficiency and/or portosystemic shunts. The clinical picture of HE varies from minimal and subclinical to pronounced manifestations, which can result in a coma [1, 2].

The pathogenesis of HE has not been completely deciphered. It is complex and involves many factors. In recent years several hypotheses

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have been discussed, but much of the evidence points to ammonia as the main cause of impaired brain function, and researchers have focused on developing therapies for hyperammonemia [3, 4]. However, despite the understanding of the importance of the role of ammonia in the pathogenesis of HE, its elevated level in the blood is not as essential for its development as the amount of ammonia penetrating the blood–brain barrier (BBB) [5].

Ammonia and Its Metabolism

Ammonia is the final product of nitrogen metabolism in the human body. Under normal conditions, the balance of nitrogen and ammonia is constantly maintained. Up to 60% of ammonia is formed in the liver with deamination of glutamine and other amino acids. A small amount is produced by the decay of glutamine in the small intestine and in the muscles during exercise. In addition, the gut microbiota decomposes protein and urea, which as a result also produces a certain amount of ammonia [6].

In the blood of a healthy person, the normal level of ammonia (NH_3) varies from 15 to 60 μg / 100 ml (21–50 μmol/l). In tissues and intercellular fluids normally, ammonia is usually proton-bound and presents in an ionized form — ammonium ion (NH_4^+). The concentration of unionized NH_3 is negligible (about 1%), and it does not penetrate the BBB. Ammonium ion content in fresh plasma is less than 20 μg per 100 ml, which confirms the extraordinary effectiveness of biochemical reactions for the removal of this highly toxic substance.

There are several mechanisms involved in ammonia neutralization, the main one of which undergoes in the periportal hepatocytes. In the Krebs-Henseleit urea cycle, about 30 g of urea is thus formed from 100 g of protein supplied with food, which is excreted by the kidneys. In addition, ammonia is metabolized by the formation of glutamine from glutamate in perivenous hepatocytes, muscles and in the brain (in astrocytes), as well as by the amination of alpha-keto acids in the synthesis of amino acids [3, 6].

Causes of Hyperammonemia

A heightened level of ammonia in the blood is defined as hyperammonemia. Being a toxic compound, ammonia is present in the blood of a healthy person in relatively low concentrations, but even a slight increase has an adverse effect on the body, and, above all, on the central nervous system (CNS). Symptoms of poisoning are manifested when the ammonia level is exceeded by 2–3 times.

In actual clinical practice, there are two main types of hyperammonemia:

1. Acquired hyperammonemia caused by the development of hepatic cirrhosis (HC) and/or portosystemic shunts.
2. Hereditary hyperammonemia resulting from various genetic defects in the enzymes of the urea formation cycle.

Increased level of ammonia in the blood is an indicator of the change of its metabolism in the liver. In previous studies, when a patient is suffering from non-alcoholic fatty liver disease (NAFLD) at the stage of steatosis and at cirrhosis, the activity of the enzymes in the urea synthesis cycle and the synthesis of glutamine in hepatobioptates thus decrease by 20% and 50%, respectively, in comparison with healthy individuals [7, 8]. An increase in the blood ammonia level is associated with various pathological conditions or disorders of physiological functions [1, 2, 9].

Hyperammonemia is typical not only for patients with hepatic insufficiency. It can be observed when there is bleeding from various parts of the gastrointestinal tract in patients without HC as well as in patients suffering from heart failure, pulmonary heart disease, leukemia, certain endocrine disorders (decompensated diabetes mellitus, severe thyrotoxicosis), patients underwent bypass surgery, etc.

In addition, an elevated level of ammonia is noted in patients suffering from Reye's syndrome (acquired deficiency of the enzymes of the ornithine cycle of urea synthesis and, as a consequence, microvesicular steatosis), disorder of liver perfusion, metabolic alkalosis and acidosis,

bacterial overgrowth syndrome, and prolonged constipation.

Hyperammonemia can be observed in any pathological conditions that are accompanied by increased protein catabolism (those suffering from extensive burns, compression or crush syndrome, extensive purulent necrotic processes, gangrene of the extremities, sepsis, etc.). These disorders cause body muscle atrophy, antioxidant defense depletion, as well as significantly weakened and suppressed immunity.

High protein diet, fasting, overeating, intense physical activity (mainly in men and bodybuilders), childbirth can also cause the level of this toxin to increase in the body.

The level of ammonia in the blood will increase when taking a number of medications, namely: salicylates, tetracycline, asparaginase, thiazide diuretics, valproic acid, ethacrynic acid, isoniazid, etc.

Hyperammonemia can develop due to the consumption of a large amount of alcohol together with the use of psychoactive drugs. And smoking even one cigarette increases the level of ammonia in the blood by 10 μmol/l.

Ammonia Is an Endogenous Toxin

Ammonia is one of the main neurotoxic metabolites in the human body. The increased supply of ammonia through the BBB depletes the reserves of glutamate and, on the contrary, promotes the excessive accumulation of glutamine in the brain (in the ammonia neutralization reaction via glutamine synthetase), which causes swelling and edema of astrocytes, inhibition of gamma-aminobutyric acid synthesis (GABA), and impaired transmembrane transport of electrolytes (Na^+ and K^+), thus worsening the chemical neuromediation. In addition, when ammonia is insufficiently neutralized, a decrease in the concentration of α-ketoglutarate (a product of glutamate metabolism), inhibition of transamination, and synthesis of neurotransmitters are noted. These pathological processes, along with the increase in alkalosis with hyperammonemia, increase hypoxia and decrease metabolism in astrocytes, neurons and, ultimately, lead to the development of HE [6].

In addition to its neurotoxicity, ammonia has general cytotoxic, including hepatotoxic, properties, which have been confirmed by new data obtained in the recent years [10, 11].

In a liver with only steatosis, in the absence of clinical manifestations of inflammation and hepatic insufficiency, ammonia thus induces formation of active forms of oxygen, dose-dependently decreases the cellular metabolism and proliferation of stellate cells, reduces the activity of endothelial NO synthase (eNOS), enhances the processes of fibrogenesis, disrupts intrahepatic hemodynamics and, accordingly, contributes to the formation of portal hypertension.

Minimal Hepatic Encephalopathy

In the case of HE, varying degrees of neuropsychiatric symptoms that reflect changes in consciousness, intelligence, behavior and neuromuscular disorders are evaluated. There are 4 stages of HE (ranging from mild to coma). In addition, in patients with chronic liver disease (CLD) minimal hepatic encephalopathy (MHE) is also identified, in which case the detection of neuropsychiatric symptoms requires the performance of various psychometric tests, and no clinical manifestations of HE are found as the result of routine clinical examination. This, first of all, can concern patients with CLD at the precirrhotic stage. Earlier, MHE was defined as latent or subclinical HE.

Evidence of the presence of MHE is the cognitive impairment that is revealed during the course of testing of the speed of psychomotor reaction / executive functions, or neurophysiological changes without clinical signs of mental changes. Such patients have decreased attention span, operative memory, difficulty in making decisions, decreased ability to drive a car, and altered handwriting. In general, the appearance of MHE worsens the quality of life and increases the risk of developing clinically pronounced HE.

A lot of tests have been proposed for the detection of MHE. In routine clinical practice, the number connection test (NCT), the digit-symbol

substitution test, and the line tracing test have become the most widely adopted [1]. They reveal an impairment of visual-spatial orientation, lowered cognitive processing speed, and decreased accuracy of fine motor skills in patients. To reduce the learning effect, the determination of visual evoked potentials (VEPs) of the brain, the critical flicker-fusion frequency (CFF) are also used for the purpose of dynamic estimation of MHE. In addition, the so-called "Repeatable Battery for the Assessment of Neuropsychological Status" (RBANS) is used in scientific research to evaluate neuropsychological status, including a test for the examination of eyesight, memorization of multisense words from the list, text (story) or numbers, association test, pattern copying, counting backwards or with an interval of 3, different scales (anxiety, depression, sleep disorders) [12, 13]. Training models are also developed in the form of either computer games or training programs that recreate real situations, which can be used to diagnose MHE when the following symptoms are manifested: decreased attention, delayed decision-making, and decreased ability to drive a car.

Hepatic Encephalopathy in Chronic Liver Diseases in Pre-Cirrhotic Stage: Clinical Reality?

No one has any doubt about the possibility of developing HE in patients with HC. To identify it, various methods are used, but the clinical manifestations of HE may not be obvious, which makes it difficult to estimate its incidence and prevalence rates. At the time when HC is diagnosed, the prevalence of apparent HE is 10–14% [14]. MHE occurs in 20–80% of patients with HC [15, 16]. However, in routine clinical practice, some patients with CLD in the pre-cirrhotic stage note a decrease in memory and attention, mood change, loss of interest in previously important personal values, etc. These patients also have difficulties making decisions and make frequent mistakes while driving a car. These manifestations require interpretation, and other causes that can lead to these disorders (in particular, vascular pathology, metabolic or electrolyte disorders, mental disorders, etc.) must be excluded.

Studies from recent years have allowed us to accumulate data on the diagnosis of MHE in patients with steatosis, chronic hepatitis C (CHC) and B (CHB), alcoholic and non-alcoholic steatohepatitis (NASH), and they have also allowed us to determine hyperammonemia in patients with initial liver changes [17–20] that cause cognitive impairment, which are manifested in particular in stressful situations that require a decision to be made [17–21].

For example, in our psychometric tests 78% (109/140) of the patients with different stages of fibrosis, including patients with chronic hepatitis, had a significant increase in the NCT time, and 40.7% (57/140) exhibited a drop in the frequency of perceived VEPs flickers (HEPAtonorm™ Analyzer, Germany) [18]. A negative correlation ($r = -0.53$, $p < 0.01$) was obtained between the frequency by which VEPs flickers were perceived and the NCT time, as well as between their changes as HE became more pronounced. Using the spectrophotometric method of ammonia determination, it was possible to record its elevated content in venous blood (up to 89 μg/dl) in 57/78 (78.1%) patients with CLD with pre-cirrhotic stage (CH), which may be the cause of MHE development in this group.

Correction of hyperammonemia in patients with CLD in the pre-cirrhotic stage was performed with L-ornithine-L-aspartate (LOLA) at a dose of 15 g of granulate per day for 2 weeks. The ammonia level normalized, and the obtained results of psychometric tests improved [18].

Evidence of the presence of MHE in patients with CHC includes cognitive impairments, which are manifested by the decreased ability to concentrate when driving a car [21].

In order to establish the connection between the frequency of violations of the Traffic Rules (TrR) and the presence of minimal signs of liver damage, the "Smart Radar" study was performed. Sixty men with symptoms of low activity MHE and CHC were examined. All patients regularly drive a car. NCT was performed, CFF and NH_4^+ content in plasma were determined, and data on the frequency of TrR violations were analyzed. All patients with CHC received LOLA at

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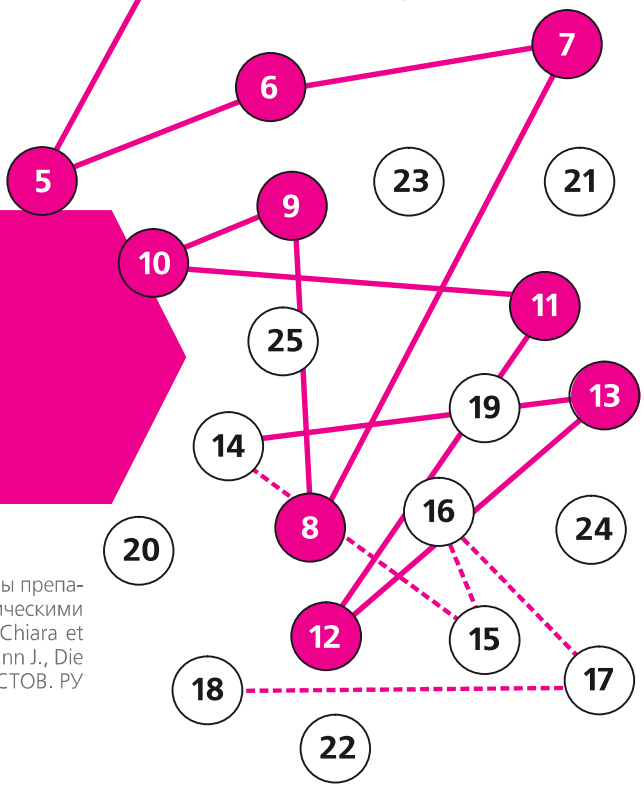

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*Е. А. Агеева, С. А. Алексеенко «Опыт применения пероральной формы препарата «L-орнитин-L-аспартат» при гипераммониемии у больных с хроническими заболеваниями печени на доцирротической стадии». **R.Jalan, F.De Chiara et al. J.Hepatology 2016 vol.64 p. 823-833. ***Grungreiff K., Lambert-Baumann J., Die Medizinische Welt, 2001; 52: 219-226. ИНФОРМАЦИЯ ДЛЯ СПЕЦИАЛИСТОВ. РУ в РФ: П № 015093/01 от 22.03.2007

a dose of 12 g/day every 2 months followed by a break of 2 months. The duration of the study was 12 months. As a result of the therapy, patients with CHC were able to improve their concentration while driving vehicles: the frequency of violations of TrR, the time of performance of the NCT were significantly reduced, and there was an increase in CFF in comparison with members of the healthy control group. In addition, the mean concentration of NH_4^+ decreased in plasma (from 141.8 ± 35.8 μM to 91.8 ± 32.6 μM, $p < 0.003$) [21].
When fractional LOLA therapy was performed, a decrease in the ammonia content, improvement of cognitive functions and, as a result, a reduction in the frequency of violations of TrR (one of the leading symptoms of MHE) was thus all observed.

In another study, the effectiveness of different treatment options using the oral LOLA form was evaluated with hyperammonemia in 37 patients with NAFLD and CHC who had stages 1–2 fibrosis [20]. Six months after the first course of therapy (9 g/day for 4 weeks), the level of ammonia in the venous blood that was determined using the enzymatic method was maintained within reference values in 25 patients. Twelve (32.4%) patients with newly detected hyperammonemia underwent a second course of treatment with the same daily dose for 10 days per month for 12 weeks. After the completion of the therapy in this group of patients, the level of ammonia in the blood decreased to 25.4 ± 1.9 μmol/l, which corresponded to the parameters of the control group of healthy individuals [20].
Important conclusions have been drawn that hyperammonemia occurs in patients with CLD (NAFLD and CHC) at the pre-cirrhotic stage; there is a recurring course of hyperammonemia, and the use of the oral form of LOLA effectively reduces the level of ammonia in the blood with different courses of treatment.
The progression of fibrosis is the key mechanism leading to the development of HC and its complications, which contributes to increased mortality in patients with NAFLD. In this regard, a decrease in the level of ammonia, as a hepatotoxin, may become a new target in the treatment of non-alcoholic steatohepatitis [22].

"Hepatoprotective" Properties of LOLA

LOLA has a number of positive properties, which allow us to classify it as one of the medicines that have hepatoprotective properties (complete absorption, presence of the effect of first pass through the liver, suppression of fibrogenesis, natural metabolism in the liver disorder, lack of toxicity, etc.) [23].
In hepatocytes, ornithine-aspartate promotes an increase in the synthesis of NAD (nicotinamide adenine dinucleotide) and prevents the decrease in the content of ATP (adenosine triphosphate) as a result of decreased cytolysis under the influence of alanine, which is synthesized via the metabolism of aspartate. In addition, due to transamination with α-ketoglutarate, ornithine acquires antioxidant properties [24].
Numerous studies have established the hepatoprotective properties of LOLA, which can be effectively prescribed to patients with CLD of different etiologies [25–31].

Data from a non-randomized prospective cohort study performed at multiple centers in Germany in 2001, involving 1,167 patients with CLD, including 648 patients with NASH and 253 with CH, demonstrated that LOLA was highly effective (decreased activity of alanine and aspartate aminotransferases, gamma-glutamyl transferase at 40–50%) and well tolerated [25].

During the course of clinical trials, patients with steatosis and steatohepatitis of various etiologies experienced relief of their asthenic, dyspeptic and pain syndromes and lost excess body weight, which made it possible to expand the set of indications for the use of LOLA [32]. The therapeutic efficacy of the oral form of LOLA was demonstrated, which was manifested in the improvement of the functional state of the liver, the positive effect on lipid metabolism, the reduction of cognitive impairment, and the improvement in the quality of life [27–31].
During the ornithine cycle, LOLA participates in the synthesis of arginine. When it is stimulated, nitric oxide (NO) is produced, which helps promote blood flow in the liver, muscles, brain, etc.

By affecting porto-hepatic hemodynamics, LOLA thus improves intrahepatic blood flow, which was obtained by performing polyhepatography in patients with chronic hepatitis of different etiologies, including NASH [33].

The correction of porto-hepatic blood flow disorders is an important aspect of pathogenetic therapy. Its effectiveness makes it possible to improve the regeneration of liver cells and reduce the progression of CLD.

New Possibilities for Determining Ammonia

Ammonia is one of the most important neurotoxins. However, in routine clinical practice there are no methods for identifying it in the brain. In order to identify its content in the blood, various methods have been developed: ionometric, spectrophotometric, enzymatic, etc. However, most methods of quantitative analysis of ammonia are rather laborious, since it is necessary to observe a cooling procedure and blood sampling technique. Prolonged application of a tourniquet or clenching of a fist can thus lead to an increase in its concentration and a false-positive result. In addition, the analysis should be carried out as soon as possible after blood sampling, as the concentration of ammonia increases in direct proportion to the storage period of the sample. The arteriovenous difference in the content of ammonia in the vessels, whose concentration is lower at rest in venous blood than in the arterial blood, should also be considered. It is caused by the binding of ammonia in the muscle tissue.

Rapid point-of-care testing is ideal for the quantitative analysis of ammonia. For this purpose, a portable PocketChem BA analyzer was developed, which makes it possible to determine the level of ammonia in the entire blood by microdiffusion. Ions of ammonia from a blood sample (20 μl), when applied to a test strip impregnated with a salt of boric acid, pass into the gaseous state and, when they reach the indicator (bromocresol green), change its color. The degree of color change is proportional to the concentration of produced ammonia (measuring range — 8–285 μmol/l, time of the test — 180 s). The device is extremely compact: it fits in the palm of an adult person, it is easy to operate, and it can be used by the patient himself [34].

Conflict of Interests

The authors declare no conflict of interests.

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