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РОЛЬ ПЕЧЕНОЧНОЙ ДИСФУНКЦИИ, ПРОЯВЛЯЮЩЕЙСЯ ГИПЕРАММОНИЕМИЕЙ, У ПАЦИЕНТОВ С ТЯЖЕЛОЙ ТЕРМИЧЕСКОЙ ТРАВМОЙ: КЛИНИЧЕСКИЙ ОПЫТ

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The Role of Hepatic Dysfunction Manifested by Hyperammonemia in Patients with Severe Thermal Trauma: Clinical Experience

Резюме

Введение. У пациентов с термической травмой в результате изменения микроциркуляции и дисфункции печени происходит нарушение обезвреживания аммиака, процессов его детоксикации и накопления в организме. Развивается гипераммониемия, которая усугубляет явления энцефалопатии. На сегодняшний день остаются вопросы по применению гипоаммониемической терапии у пациентов с ожогами и её влиянию на исходы заболевания. **Цель:** оценка выраженности печеночной энцефалопатии, уровня аммиака капиллярной крови и его снижения на фоне терапии у пациентов с термической травмой. **Материалы и методы.** В исследование выборочно включена группа из 29 пациентов с тяжёлой ожоговой травмой (Индекс Франка более 145 ед.), находившихся на лечении в реанимационном отделении, и группа с легкой ожоговой травмой (Индекс Франка не более 90 ед.) из 15 пациентов, находившихся в условиях коечного отделения. Выраженность печеночной энцефалопатии определяли по шкале West Haven. Уровень аммиака в сыворотке крови исследовали методом микродиффузии с применением портативного экспресс-анализатора PocketChemTM BA PA-4140. Для коррекции гипераммониемии с помощью инфузомата внутривенно вводился орнитин в дозе 80 г/сут в течение 10 дней. Все статистические расчёты выполнены с использованием программного обеспечения SPSS v27 (Statistical Package for the Social Sciences). **Результаты.** Пациенты с ожоговой травмой, согласно индексу Франка, были разделены на 3 подгруппы (1-3), глубина поражения соответствовала от 31 ед. до 91 ед. и более. Высокий уровень аммиака в крови зарегистрирован во всех трех подгруппах, а при индексе Франка 91 ед. и выше более чем у половины пациентов превышал 285 мкмоль/л. Отмечена прямая связь между индексом Франка и уровнем аммиака у пациентов с ожоговой травмой (p=0,01). Чем выше Индекс Франка, тем выше уровень аммиака в плазме крови. Данная тенденция прослеживается как до начала лечения (rs_1=0,971, rs_2=0,996), так и после начала лечения (rs_1=0,898, rs_2=0,948) по обеим группам пациентов. На 2-3-й день комбинированного лечения с включением орнитина отмечено уменьшение аммиака в крови на 20-30 % от исходного уровня во всех исследуемых группах (p <0,001). Уровень аммиака после лечения статистически

значимо снизился у всех 44 пациентов (p <0,001). **Выводы.** Печеночная дисфункция является одним из проявлений системного ответа на термическую травму. Поэтому нарушение процессов утилизации аммиака может оказывать неблагоприятное воздействие на клиническую картину в целом. Наличие дисфункции печени, высокий уровень аммиака и как следствие развитие печёночной энцефалопатии утяжеляют течение ожоговой болезни, что существенно затрудняет оказание помощи данной категории пациентов.

Ключевые слова: *термическая травма, печеночная дисфункция, гипераммониемия, печеночная энцефалопатия, лечение гипераммониемии*

Конфликт интересов

Соавтор статьи Ильченко Л.Ю. является главным редактором журнала «Архивъ внутренней медицины». Статья прошла принятую в журнале процедуру рецензирования. Решение о публикации статьи было принято редакционной коллегией без участия главного редактора. Об иных конфликтах интересов авторы не заявляли

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Abstract

Introduction. In patients with thermal injury, changes in microcirculation and liver dysfunction lead to impaired detoxification of ammonia, resulting in its accumulation in the body. This develops hyperammonemia, which exacerbates the phenomena of encephalopathy. To date, questions remain regarding the application of hypoammonemic therapy in burn patients and its impact on disease outcomes. **Aim:** To assess the severity of hepatic encephalopathy, the level of ammonia in capillary blood, and its reduction against the backdrop of therapy in patients with thermal injury. **Materials and methods.** The study selectively included a group of 29 patients with severe burn injury (IF more than 145 units) who were treated in the intensive care unit, and a group with mild burn injury (IF no more than 90 units) of 15 patients who were in the hospital ward. The severity of hepatic encephalopathy was determined using the West Haven scale. The level of ammonia in the serum was investigated by microdiffusion method using the portable express analyzer PocketChemTM BA PA-4140. For the correction of hyperammonemia, ornithine was intravenously administered via an infusion pump at a dose of 80 g/day for 10 days. All statistical calculations were performed using the software SPSS v27 (Statistical Package for the Social Sciences). **Results.** According to the Frank index, patients with burn injury were divided into 3 subgroups (1-3), the lesion depth ranged from 31 units to 91 units or more. High levels of ammonia in the blood were recorded in all three subgroups, and with a Franck index of 91 units. and higher than 285 mmol/l in more than half of the patients. There was a direct relationship between the Franck index and the level of ammonia in patients with burn injury (p=0.01). The higher the Franc Index, the higher the level of ammonia in the blood plasma. This trend can be traced both before the start of treatment (rs_1=0.971, rs_2=0.996) and after the start of treatment (rs_1=0.898, rs_2=0.948) in both groups of patients. On the 2-3 day of combined treatment with the inclusion of ornithine, a decrease in ammonia in the blood by 20-30 % of the baseline level was noted in all study groups (p <0.001). The level of ammonia after treatment decreased significantly in all 44 patients (p <0.001). **Conclusions.** Hepatic dysfunction is one of the manifestations of the systemic response to thermal injury. Therefore, disruption of ammonia utilization processes can have an adverse effect on the overall clinical picture. The presence of liver dysfunction, high levels of ammonia and, as a result, the development of hepatic encephalopathy aggravate the course of burn disease, which significantly complicates the provision of care to this category of patients.

Key words: *thermal injury, liver dysfunction, hyperammonemia, hepatic encephalopathy, treatment of hyperammonemia*

Conflict of Interest

Co-author of the article Ilchenko L.Yu. is the editor-in-chief of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. The decision to publish the article was made by the editorial board without the participation of the editor-in-chief. The authors did not declare any other conflicts of interest

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Compliance with the principles of ethics

The study protocol was approved by the local ethics committee (Minutes No 3-25 dated 05.09.2025). Approval and protocol procedure was obtained according to the principles of the Declaration of Helsinki. Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

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BAS — biologically active substances, DIC syndrome — disseminated intravascular coagulation syndrome, IL-6 — interleukin-6, FI — Frank's index, VLDL — very low density lipoproteins, HE — hepatic encephalopathy, TG — triglycerides, TBSA — total body surface area.

Background

A thermal injury is one of the most common severe trauma categories in the modern world. Pathophysiology of a thermal damage is a complex mechanism, and it depends on a number of factors: burn area (damaged body surface area), depth of the damage and inflammation intensity, which is quantified by Frank's index (FI), a prognostic index of burn injury severity used to forecast mortality among patients.

Burns covering over 30 % of the total body surface area (TBSA) cause significant fluid depletion in combination with production and release of inflammatory mediators, which results in a systemic effect, namely in a typical cardiovascular dysfunction, known as burn shock. Pathophysiologically, microcirculation is disturbed as a result of a vascular spasm due to pain and stress response of the body. A huge amount of catecholamines is released in the bloodflow. Arteriolovenular and arteriovenous shunts open, and cardiac shunt occurs, bypassing the microcirculatory bloodstream. Effects of high temperatures in a thermal injury lead to red blood cell hemolysis; protein is lost through the wound bed, and moisture is evaporated from the burned surface. Biologically active substances (BAS), kinins, toxic tissue degradation products accumulate in the body and cause increased vascular permeability and cell membrane penetration. Protein and plasma leave the vascular bed and accumulate in soft tissues. Edema develops, and the blood flow to internal organs decreases. Clots are not uncommon. Pain reaction and loss of plasma are the key mechanisms in burn shock development.

In 1932, David Cuthbertson proposed a theory of metabolic response to a severe trauma comprising two phases: "flux" and "reflux" [1]. The reflux phase is associated with hypermetabolism, hematogenic shock and reduced oxygen supply and consumption. The flux phase is the key in body recovery after a thermal trauma. Numerous clinical manifestations, including muscle mass loss resulting from metabolic response during the flux phase, are related to organ dysfunction in patients with severe burns.

In 2011, Wenzhong Xiao et al. [2] published an article describing a shift in human immune cells during the first 12 hours after the injury, which is the worst in burns.

In deep burns covering over 30 %, severe stress response of the body can be observed. Catecholamines are released; they cause hypermetabolism, ischemia of peripheral tissues, slow wound healing, and immunosuppresion. The probability of sepsis, multisystem organ dysfunction and death increases. Hypermetabolic reaction at the cellular and systemic levels is harmful. At the systemic level, the structure and functions of the vital organs (heart, liver, skeletal muscles, skin), immune system and transmembrane transport system are jeopardise [1]. Hypermetabolic processes, inflammatory reaction associated with protein breakdown, aminoacid degradation, insulin resistance, hyperglycaemia, and lipolysis, contribute to the development of organ failure, first of all, of the liver [3–6]. A severe burn triggers proinflammatory processes, hypoperfusion, edema and facilitates hepatic cell apoptosis.

Homeostasis of the most important nitrogen-containing intermediate products, ammonia and glutamine, is a strictly regulated process, where teh central role is played by the intestines/liver axis [7]. Following a thermal trauma, the rate of blood flow to intestines drops by almost 60 % vs. initial values and remains hypoxic for approximately four hours. It can be assumed that the hepatic blood flow rate also drops, causing programmed cell death [5]. All this eventually leads to hepatic dysfunction.

A thermal injury causes homeostasis disturbances, which results in an inflammatory response aimed to restore the initial condition of the body. The liver is one of the vital organs responding to a thermal injury.

Studies showed that, immediately after a burn, liver damage can be associated with massive edema of hepatic parenchyma, as evidenced by hypoalbuminemia. All this is proven by a burn model in rats, where it has been demonstrated that 2–7 days after a thermal trauma, the liver weight increases significantly [8]. Numerous studies emphasise that hepatomegaly persists for three weeks after a burn. As early as one day after a trauma, signs of cholestatic and cytolytic syndromes can be observed [8].

Lower production of protein components of very low density lipoproteins (VLDL), that carry triglycerides (TG) and fatty acids, reduces their release by the liver, which can lead to adipose infiltration of this organ. It further increases the risk of sepsis. Besides, extrahepatic tissue uses less TG as an energy substrate [1, 4].

Adipose infiltration is a common event and is usually reversible. Nevertheless, it has been demonstrated that it is associated with increased bacterial translocation, hepatic failure and endotoxemia, and the liver has the critical role in response to a thermal injury [6, 9].

Following a serious trauma, such as a severe burn, hepatic protein synthesis shifts from hepatic housekeeping proteins (albumin, prealbumin, transferrin and retinol-binding protein) to acute phase proteins, which act as inflammation mediators; they function as transport proteins and participate in burn wound healing [3]. At the same time, interleukin-6 (IL-6), an essential mediator of an acute inflammation phase response, is synthesised in the liver by fibroblasts, Kupffer cells and activated monocytes, macrophages, vascular endothelial cells, microglial cells and astrocytes.

J. Albrecht, M.D. Norenberg (2006) [10] proposed the Troic horse hypothesis, according to which glutamine acts as an ammonia carrier in astrocyte mitochondria after it has been metabolised back to glutamate and

ammonia, thus resulting in oxidative stress and cellular dysfunction.

Recent studies showed that hyperammoniemia facilitates development of sarcopenia. Skeletal muscles become the main organ to metabolise ammonia, substrates of this metabolism get depleted, and muscle mass decreases. Myostatin is a potent inhibitor of autocrine increase in myocyte production, which inhibits growth of skeletal muscles and reduces muscle mass in hyperammoniemia. Hyperammoniemia induces autophagy, and damaged proteins are cleaved or digested in order to maintain cell function. It has been demonstrated that hyperammoniemia reduces skeletal muscle strength and increases muscle fatigue, resulting in marked muscle dysfunction [11].

Clinical Profile of Patients and Study Methods

This study was conducted in 2024–2025 at A.V. Vishnevskiy National Medical Research Center of Surgery of the Ministry of Defense.

The purpose of the study was to assess the intensity of HE, capillary ammonia levels and their reduction in patients with thermal injuries.

The study included two groups of patients. Group 1 included 29 male patients aged 18 to 54 years old (36±18), admitted to ICU with severe burns. The total burn area exceeded 40 % of the body surface; deep burns comprised over 35 %, Frank's index was 145 units and over. All patients were in burn shock: 21 patients had severe shock and 8 patients has extremely severe shock. Group 2 (patients with minor burns) included 15 patients in a general ward aged 20 to 44 years old (32±12). The total burn area was less than 40 % of the body surface; deep burns comprised 5–10 %, Frank's index was 31–90 units.

Blood ammonia levels were measured with the help of a portable rapid-response analyzer PocketChemTM BA PA-4140, which was registered in Russia in 2018. The analyser measures ammonia levels within 180 seconds. The advantage of this method is the use of dry chemicals; the method is based of the microdiffusion method, which ensures high precision of measurements. The measurement range is 8 μmol/L to 285 μmol/L. Normal blood ammonia levels are not more than 60 μmol/L. In this study, capillary blood was sampled in accordance with the study method.

All patients underwent therapy in accordance with the clinical guidelines "Chemical and thermal burns. Sunburns. Airway burns", prepared by the Combustion Association World Without Burns and approved by the Ministry of Health of the Russian Federation in 2024 [12]. Also, ornithine 80 g daily was injected for 10 days using a pump system, in order to reduce blood ammonia levels.

Statistical data processing was performed with the help of SPSS v27 (Statistical Package for the Social Sciences). Sampling characteristics were described using descriptive statistics methods: calculation of mean (M), standard deviation (SD), median value. The relationship between Frank's index and blood ammonia concentrations was assessed using correlation analysis: Pearson's correlation coefficient and Spearman's rank correlation (rs1 — group 1, rs2 — group 2). Correlation was considered significant at 0.01 (bivariate correlation).

Wilcoxon rank sum test was used to analyse blood ammonia levels before and after therapy in both groups of patients. The study continued with comparison of the intensity of each parameter: Frank's index, ammonia concentration before and after therapy using Mann-Whitney U-test. Differences were statistically significant at $p < 0,05$.

Results and Discussion

One of the most important functions of the liver is ammonia detoxication, which is impaired in patients with thermal traumas. Ammonia is a toxic substance, the majority of which is present in blood in its ionised form ($NH4+$). In healthy individuals, fasting blood concentrations are low (8–60 μmol/L) [13].

Ammonia is a waste product of inorganic nitrogen, which is metabolised and produced by all tissues. In healthy individuals, ammonia is produced mainly in intestines as a result of three key mechanisms: urea hydrolysis by bacterial urease, bacterial protein deamination and glutamine metabolism in intestinal mucosa [8]. Stomach, small intestine and colon participate in ammonia exchange; however, the central role in this process belongs to the liver. It is the main sorce and place of its inactivation.

Five urea cycle enzymes (carbamoyl phosphate synthetase, ornithine-carbamoyl-transferase (ornithine transcarbamylase), argininosuccinate synthetase, arginine succinate lyase, and arginase (arginine hydrolase)) participate in convertion of toxic ammonia into non-toxic urea, which is excreted in urine. Unprocessed ammonia is transported with blood to pericentral hepatocytes for efficient ammonia detoxication in the liver due to activity of glutamine synthetase, which converts ammonia into glutamine, thus completing the intrahepatic cycle of glutamine [8]. When these processes are disturbed, a serious manifestation of hepatic dysfunction develops, which presents as higher ammonia levels.

Ammonia affects neurons and astrocytes, star cells, immune cells, myocytes, hepatic cells, etc. Astrocytes are the only cells in the brain, which contain glutamine synthetase, an important enzyme of the glutamatergic system. Therefore, then ammonia concentrations in teh brain rise, these glial cell start removing it by converting

glutamate into glutamine, catalysed byglutamine synthetase. Ammonia has toxic effects on hepatic cells. In the presence of ammonia, gluconeogenesis, lycogenolysis, glycolysis, and ketogenesis are inhibited. The main sources of energy balance are damaged, and brain neurons are de-energised as a result of insufficient amount of substrates. Oxidative stress develops, which causes inflammation, intracellular edema and cell death.

Higher blood ammonia levels are an important factor of hepatic encephalopathy (HE) [14]. HE means neuropsychic disorders developing in patients with damaged liver, resulting from peripheral blood shunt and impaired deintoxication function of the liver [15, 16]. In patients with HE and burns, the rate of ammonia elimination by the liver drops significantly. Higher blood ammonia levels result in ammonia penetration through the hematoencephalic barrier, contributing to neurotoxic effects.

All patients with thermal burns were distributed as follows:

Frank's index: 1) 31 to 60 units — 7 patients; 2) 61 to 90 units — 8 patients; 3) 91 units and over — 29 patients. Quantitative parameters of ammonia in group 1 and group 2 were considerably lower than in sub-group 3 (Fig. 1). An evaluation of the correlation between ammonia concentration and Frank's index showed significant positive correlation (p=0.01) in both groups of patients. There is direct relation between Frank's index and ammonia concentration. The higher Frank's index is, the higher plasma ammonia levels are. This trend is observed both prior to therapy (rs1=0.971, rs2=0.996) and after therapy (rs1=0.898, rs2=0.948) in both groups of patients.

Hepatic encephalopathy grades. HE stages can be assessed using capillary ammonia levels: 1) increase of up to 1.33 times of the upper limit of normal (corresponded to West Haven HE stage 1); 2) increase of 1.33–1.67 times of the upper limit of normal corresponded to West Haven HE stage 2); 3) increase of 1.67–2 times of the upper limit of normal (corresponded to West Haven HE stage 3); 4) over 2 upper limits of normal (corresponded to West Haven HE stage 4).

Out of 15 patients with minor burns, 5 had stage 1 hepatic encephalopathy: errors in calculation (addition), ammonia level was 1.33 times higher than the upper level of normal; number connection test run for 31–50 seconds. 10 patients had stage 2 hepatic encephalopathy: minimal temporal and spatial disorientation, abnormal behaviour, errors in calculation (subtraction), ammonia level was 1.33–1.67 times higher than the upper level of normal; number connection test run for 51–80 seconds.

In patients with severe thermal injuries treated in ambustial ICU, the only method to evaluate HE (West Haven scale) is to measure ammonia concentration. On the basis of ammonia levels, 29 patients had teh following distribution: 1 patient had stage 2 HE, 4 patients — stage 3 HE, and 24 patients — stage 4 HE.

It has been established that all 29 patients with severe burns had higher urea levels (over 8.1 mmol/L). It is most likely a consequence of patients' state of shock and decreased filtration capacity of kidneys, which is supported by high blood creatinine concentrations (150 μmol/L and higher). In patients with minor burns, 8 patients had normal urea levels, while 7 patients had over 8.1 mmol/L.

The purpose was to evaluate the efficacy of the modern drug therapy for correction of hyperammoniemia, used in hepatology, when used in patients with burns. Contemporary therapeutic methods aim to reduce ammoniogenesis, absorb ammonia in the digestive tract, activate ammonia excretion by urogenesis activation after primary disease correction or addition of intermediate products of urea cycle and glutamine synthesis [17]. For the therapy, a hepatotrophic product, possessing hypoammoniemia properties, was used, where the active substance was ornithine.

Ornithine has detoxication properties; it reduces high ammonia levels in the body or liver dysfunction. The mechanism of its action is associated with participation in the Krebs urea cycle (activates the cycle function and restores hepatic cell enzyme activity: ornithine carbamoyltransferase and carbamoyl phosphate synthetase).

All examined patients (44 individuals) with thermal traumas received hypoammoniemia agents. The drug resulted in reduction in ammonia levels by 20–30 % vs. baseline on day 2–3 of therapy ($p < 0.001$). Following therapy, ammonia levels were significantly lower in all 44 patients ($p < 0.001$). Patients with minor burns: 1) before therapy: M = 74.8 (95 % CI 71.15–78.45), SD = 6.59, median = 75 (95 % CI 71–81); 2) after therapy: M = 56.67 (95 % CI 53.42–59.91), SD = 5.86, median = 57 (95 % CI 52–62); 3) FI: M = 55.93 (95 % CI 48.63–63.24), SD = 13.19, median = 62 (95 % CI 51–69). Patients with severe burns: 1) before therapy: M = 227.66 (95 % CI 198.72–256.59), SD = 76.08, median = 268 (95 % CI 241–281); 2) after therapy: M = 169.55 (95 % CI 138.94–200.16), SD = 80.47, median = 175 (95 % CI 110–204); 3) FI: M = 176.41 (95 % CI 163.64–189.19), SD = 33.58, median = 167 (95 % CI 155–191). Significant differences were observed for all variables ($p < 0.001$).

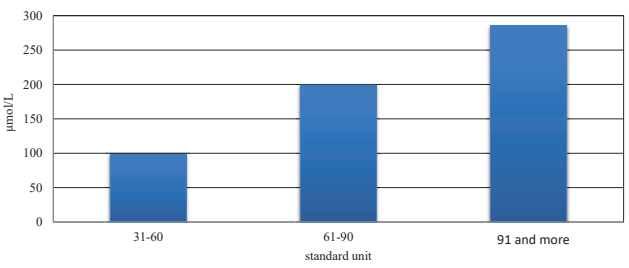

Figure 1. *Relationship between ammonia level (μmol/L) and Frank index (standard unit) in patients with thermal injury*

Evaluation of effects of therapy was possible in 15 controls. 10 days after therapy initiation, all patients had West Haven HE stage 0 to 1; ammonia levels in all patients were below 73 μmol/L.

Conclusion

Hepatic dysfunction is a systemic response to a thermal trauma. Impaired ammonia utilisation results in hyperammoniemia. No doubt that the liver is essential for the organisation and regulation of metabolic processes in patients with burns, therefore hepatic dysfunction can have an unfavourable impact on the clinical presentation in general.

Systemic inflammatory response is a pathogenetic foundation for multiorgan failure in patients with thermal injuries. Progressing dysfunction and resulting organ and system insufficiency are main clinical presentations of burn disease and the key cause of mortality. The main reasons are severe systemic inflammation, including burn shock, progressive disseminated intravascular coagulation syndrome (DIC syndrome), and purulent-septic complications [18, 19].

This study demonstrates that, together with existing multiorgan failure, hepatic dysfunction develops, which leads to high blood ammonia levels in patients with thermal injuries. West Haven scale used in patients with hepatic pathologies can help in assessing the intensity of hepatic encephalopathy in this group of patients.

The study of the ammonia effects on the clinical presentation and mortality, as well as development of the ways to correct hyperammoniemia in patients with severe burn trauma require additional research in this area.

Вклад авторов:

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