Review article

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Changes in the neuro-glial-vascular interface in metabolic intoxications in children (based on acetonemic syndrome and hyperammonemia)

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Objective: To investigate morphofunctional changes of the neuro-glial-vascular interface in children with metabolic intoxications, particularly in acetonemic syndrome and hyperammonemia.

Materials and methods: A systematic literature review with elements of narrative analysis was conducted following PRISMA guidelines. Literature search was performed in PubMed/MEDLINE, Web of Science Core Collection, Scopus, and Cochrane Library for the period 1990-2024. Included studies involved children from birth to 18 years and investigated neurotoxic effects of acetonemic syndrome and hyperammonemia. Study quality was assessed using Newcastle-Ottawa Scale, AMSTAR-2, and SYRCLE tools.

Results: Key morphofunctional disorders of the neuro-glial-vascular interface were identified: cytotoxic astrocytic swelling due to glutamine accumulation during ammonia detoxification; blood-brain barrier disruption with decreased expression of tight junction proteins (claudin-5, occludin, ZO-1); impaired energy metabolism due to glycolysis inhibition and mitochondrial dysfunction; excitotoxicity resulting from glutamate-glutamine cycle disruption; microglial activation with increased expression of CD68, Iba1, MHC II, and pro-inflammatory cytokine secretion.

Conclusions: Morphofunctional changes of the neuro-glial-vascular interface with acetonemic syndrome and hyperammonemia are characterized by complex disruptions of blood-brain barrier (BBB) structure and function, energy metabolism, neurotransmitter balance, and neuroinflammatory processes. A personalized approach to diagnosis and treatment using biomarkers of BBB damage and neuroinflammation is necessary.

Keywords: *neuro-glial-vascular interface; acetonemic syndrome; hyperammonemia; blood-brain barrier; astrocytes; excitotoxicity; neuroinflammation; children*

Relevance

Metabolic intoxications in children, particularly acetonemic syndrome [3] and hyperammonemia [1, 2, 10], represent a serious clinical problem in pediatrics. "Prolonged hyperammonemia causes irreversible damage to the central nervous system leading to cortical atrophy, ventricular system enlargement, and inhibition of myelination processes, which can subsequently result in cognitive impairments, seizures, and cerebral palsy" [1, 2]. In turn, "acetoacetate and beta-hydroxybutyrate stimulate the activity of the Na-K-Cl cotransporter in endothelial cells of brain microvessels, making them more susceptible to damage" [58].

One of the most vulnerable targets in such conditions is the neuro-glial-vascular interface—a complex morphofunctional system that provides metabolic, barrier, and signaling interactions between neurons, glial cells (primarily astrocytes), and the brain's capillary network [4, 7]. Under normal conditions, this interface regulates the permeability of the blood-brain barrier (BBB), ensures substance exchange between blood and nervous tissue, maintains ionic balance, participates in the detoxification of neurotransmitters (particularly glutamate) and neutralizes ammonia through the synthesis of glutamine in astrocytes [4, 5, 6].

Morphologically, the neuro-glial-vascular interface consists of endothelial cells and their associated pericytes, astrocytes, neurons, and microglia [7]. Under physiological conditions, astrocytes are in close interaction with the endothelium, regulating metabolism and protecting neurons from toxic influences [4, 7]. Their ability to bind excess ammonia and maintain the acid-base homeostasis of brain tissue is of particular importance [9].

In acetonemic syndrome, due to the accumulation of ketone bodies, and in hyperammonemia—because of the excessive concentration of ammonia in the blood and tissues— the function of this interface is disrupted [9, 10]. Toxic metabolites penetrate the BBB [12], causing astrocyte swelling [13, 23, 24], sodium-potassium pump dysfunction [14], impaired glucose transport [15], activation of microglia, and increased production of pro-inflammatory cytokines (IL-1β, TNF-α) [16]. This is accompanied by neurotransmitter imbalance [17], loss

of BBB integrity [18], decreased neuronal activity, and eventually the development of encephalopathy, seizures, impaired consciousness, and delays in cognitive and psychomotor development.

Particularly concerning is the fact that, the neuro-glial system is morphofunctionally immature in childhood, and the BBB has increased permeability, which enhances the brain tissue's sensitivity to metabolic toxins [19]. Moreover, the compensatory capacity of a child's body is still limited, and signs of intoxication may develop rapidly, even with short-term exposure [20].

Despite the high clinical significance of these conditions, the morphofunctional changes of the neuro-glial-vascular interface in various forms of metabolic intoxication in children remain poorly understood [21]. The lack of clear understanding regarding the nature and dynamics of these changes prevents early detection of CNS damage, complicates prognosis, and hampers the development of personalized therapeutic approaches [22]. Therefore, targeted research into structural and functional changes of the neuro-glial-vascular interface in children with acetonemic syndrome and hyperammonemia becomes especially relevant, as it may improve diagnosis, prevent severe outcomes, and optimize the management of patients with metabolic crises.

Research objective

To analyze scientific approaches and review current literature on the morphofunctional changes of the neuroglial-vascular interface in children with metabolic intoxications (based on acetonemic syndrome and hyperammonemia) in order to identify the mechanisms of central nervous system damage, improve early diagnosis of neurotoxic complications, and substantiate approaches to personalized therapy**.**

Materials and methods

A systematic literature review with elements of narrative analysis was conducted to investigate the morphofunctional changes in the neuro-glial-vascular interface in children with metabolic intoxications, particularly in cases of acetonemic syndrome and hyperammonemia. The study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews. Literature sources were searched in the following electronic databases: PubMed/MEDLINE, Web of Science Core Collection, Scopus, and Cochrane Library for the period 1990–2024, with additional searches performed via Google Scholar. English-language keywords and term combinations were used in the search, including "acetonemic syndrome," "hyperammonemia," "blood-brain barrier," "astrocyte swelling," "excitotoxicity," "neuroinflammation," and relevant MeSH terms.

The review included publications that met the following inclusion criteria: original studies, systematic reviews, and meta-analyses published in English; studies involving children from birth to 18 years of age; papers investigating the neurotoxic effects of acetonemic syndrome and/or hyperammonemia; and research on morphofunctional changes of the BBB in metabolic disorders. Experimental studies on animal models relevant to pediatric practice were also included. Exclusion criteria were as follows: conference abstracts without full texts, case reports with fewer than three patients, studies exclusively involving adult populations, publications unrelated to the neurotoxic effects of the studied syndromes, and duplicate publications.

The selection of sources was carried out in two stages: an initial screening based on titles and abstracts using the inclusion/exclusion criteria, followed by full-text review of the selected articles. Each study was independently assessed by two reviewers, with discrepancies resolved through discussion until consensus was reached. Additional relevant studies were identified through manual searches of reference lists from selected articles.

To assess the quality of the included studies, the following tools were used: the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, AMSTAR-2 for systematic reviews, and SYRCLE's Risk of Bias tool for animal studies. Evaluation criteria included methodological quality, appropriateness of study design to objectives, adequacy of statistical analysis, presence of control groups, and sample representativeness.

From each included publication, the following data were extracted: study characteristics (authors, year, country, design), population details (age, sex, sample size), research methods and diagnostic criteria, main findings and conclusions, and study limitations. A qualitative (narrative) synthesis of the data was conducted, with thematic grouping into the following categories: morphological changes of the neuro-glial-vascular interface, pathophysiological mechanisms of BBB disruption, disturbances in energy metabolism, neurotransmitter imbalances and excitotoxicity, inflammatory processes and microglial activation, clinical manifestations and diagnostic approaches, and therapeutic strategies.

Due to the heterogeneity of the included studies, a quantitative meta-analysis was deemed inappropriate.

Results

Changes in the structure of the neuro-glial-vascular interface in acetonemic syndrome and hyperammonemia are of key importance in the development of neurological symptoms and the progression of encephalopathy [1–10, 13, 15].

Morphofunctional disorganization of the neuro-glial-vascular interface. This interface, composed of neurons, astrocytes, endothelial cells of capillaries, pericytes, microglia, and the basal membrane, performs essential functions in metabolic exchange between blood and nervous tissue, regulation of BBB permeability, and maintenance of brain homeostasis [1–10, 13, 15]. In metabolic disorders characteristic of these syndromes, the BBB undergoes significant morphofunctional disorganization [20]. One of the earliest and consistent histological manifestations found in scientific studies is pronounced astrocyte swelling [1–10, 13, 15]. Biochemically, this phenomenon is caused by an excess of ammonia in the blood, which freely passes through

This article contains some figures that are displayed in color online but in black and white in the print edition

the BBB and enters brain tissue [1, 2, 5, 6, 9, 23, 24]. In the brain, ammonia is detoxified in astrocytes through the activity of the enzyme glutamine synthetase, which catalyzes the reaction of glutamine formation from glutamate and ammonia [1, 2, 5, 6, 9, 23, 24]. It has been proven that glutamine synthesized in large amounts can accumulate in astrocytes, creating osmotic pressure that leads to water influx into the cell and the development of intracellular (cytotoxic) edema [13]. Morphologically, this process is accompanied by an increase in astrocyte volume, destruction of their processes, deformation of contacts with capillaries, which impairs the metabolic support of neurons [23, 24].

Impairment of BBB function. Alongside the aforementioned changes, there is also a disruption in the functional state of the BBB [1–10, 13, 15]. With an excess of ketone bodies (in particular, β-hydroxybutyrate and acetoacetate) and ammonia, damage to endothelial cells of capillaries is observed. It has been established that this pathological process may be caused by oxidative stress, reduced activity of cellular respiration enzymes, and the disintegration of intercellular tight junctions [25, 26, 28, 29–34].

Oxidative stress occurs when the increase in energy output produced by aerobic metabolism leads to elevated formation of potentially harmful reactive oxygen species (ROS). During incomplete O_2 oxidation, ROS such as superoxide anion radical, hydrogen peroxide, and hydroxyl radical are formed. These highly reactive compounds are capable of damaging cellular proteins, lipids, and DNA. When the ROS burden in a cell exceeds its own antioxidant capacity, a state of oxidative stress arises. In the context of metabolic disorders, elevated concentrations of ketone bodies and ammonia potentiate oxidative stress, leading to endothelial dysfunction, impaired microcirculation, and intensified inflammatory responses. This creates a vicious cycle of damage, where metabolic disorders intensify oxidative stress, and oxidative stress in turn deepens metabolic disturbances, causing progressive tissue damage [34]. At the molecular level, this process manifests as decreased expression of claudin-5, occludin, and ZO-1 proteins, leading to increased BBB permeability [31]. Histochemically, it is accompanied by extravasation of plasma proteins (albumin, immunoglobulins), which can be detected in brain tissues, as well as swelling of the perivascular space, signs of hyperemia, and leukocyte diapedesis [35]. As a result, vasogenic edema develops, leading to compression of capillaries, impaired cerebral perfusion, and worsening ischemic injury to nervous tissue [35].

Astrocytic disturbances and effects on water-electrolyte balance. Special attention is warranted for the disruption of astrocytic contacts with capillaries. Normally, astrocyte end-feet form a glio-vascular mantle that covers almost the entire surface of brain capillaries and regulates the transport of water, ions, and energy substrates, particularly through the aquaporin AQP4 [36]. It has been shown that in acetonemia and hyperammonemia, these structures become disorganized, which is either accompanied by a decrease in AQP4 expression (disrupting osmoregulation) or by compensatory upregulation (which, conversely, enhances astrocyte swelling). Both mechanisms lead to pathological accumulation of fluid in brain tissue and disruption of metabolic exchange between neurons and capillaries, as reflected in the study by Rama Rao K. V. et al. [37]. To determine the potential role of aquaporins in astrocyte swelling, the authors measured AQP4 protein expression in cultured astrocytes exposed to 5 mM NH_4Cl. It was found that AQP4 levels significantly increased 10 hours after ammonia treatment and showed progressive growth up to 48 hours, preceding the onset of astrocyte swelling. The researchers concluded that AQP4 may be involved in astrocyte edema associated with hyperammonemic conditions [37].

Energy metabolism in neurons and astrocytes in acetonemia and hyperammonemia. The primary energy source for brain cells, particularly neurons and astrocytes—which require constant energy supply for maintaining electrical excitability, synaptic transmission, and osmoregulation—is glucose [38]. Its transport to brain tissue is facilitated by transporters—mainly GLUT1 in capillary endothelium and astrocytes [39], and GLUT3 in neurons [39]. Under acetonemia, there is competition for BBB transport between glucose and ketone bodies (especially β-hydroxybutyrate), which may reduce glucose entry into the brain [40].

Simultaneously, due to excess ammonia accumulating in brain tissue, the activity of the key glycolytic enzyme phosphofructokinase decreases, which further worsens ATP production. In astrocytes, energy flow is redirected toward ammonia detoxification (via the glutamine synthetase reaction), which diverts resources from supplying neurons with lactate—a key product of astrocytic metabolism necessary for neuronal function [41]. This mechanism is known as the astrocyte-neuron lactate shuttle (ANLS), which provides neurons with energy through their metabolic connection to astrocytes [41]. Normally, neuronal activity leads to glutamate release, which stimulates glycolysis in astrocytes and lactate production. Lactate is transported to neurons via monocarboxylate transporters and used as a readily available energy source. When this pathway is disrupted, particularly by the toxic effects of ammonia, lactate production and delivery to neurons decrease [41]. As a result, neurons do not receive enough energy substrate and experience energy starvation, impairing their function and viability.

A decrease in intracellular ATP levels leads to dysfunction of the Na^+/K^+-ATPase (sodium-potassium pump), which maintains the electrochemical gradient between the neuron's inner and outer membranes [42]. This pump actively removes three Na^+ ions from the cell and brings in two K^+ ions, which is necessary for restoring the resting potential after a nerve impulse. When this mechanism is inhibited, excessive accumulation of sodium in neurons and extracellular potassium is observed, which causes depolarization of the cell membrane, excessive excitability or impulse transmission blockade, and the opening of ion channels that allow uncontrolled calcium influx [42–44]. Excess intracellular Ca^{2+} activates enzyme cascades, particularly phospholipases, proteinases, and endonucleases, ultimately leading to membrane damage, DNA fragmentation, and the initiation of apoptosis or necrosis of neurons [42–44].

Neurotransmitter imbalance and its role in the development of encephalopathy. Neurotransmitter imbalance is a key pathophysiological mechanism in the development of central nervous system damage in acetonemic syndrome and hyperammonemia [2]. One of the key factors in the impairment of neuronal function in many neurological pathologies is the excessive accumulation of glutamate [2]. Glutamate activates ionotropic postsynaptic receptors—N-methyl-D-aspartate (NMDA) and AMPA/kainate receptors—causing depolarization of the neuronal membrane through the influx of Na^+ ions and the initiation of an action potential. Normally, after performing its signaling function, glutamate should be rapidly removed from the synaptic cleft [2]. If this does not occur, two pathological effects arise: excessive stimulation of receptors, which complicates the recognition of new signals and may cause cellular edema; and glutamate that escapes the synapse can activate extra synaptic NMDA receptors, causing Ca^{2+} influx and the initiation of cell death cascades [2].

Astrocytes in turn play a critical role in preventing excitotoxicity. They provide rapid glutamate clearance from the extracellular environment due to high expression of specific transporters—GLT-1 (EAAT2) and GLAST (EAAT1). These belong to the excitatory amino acid transporter family (EAAT1–5), are electrogenic and sodium-dependent, and are capable of transporting glutamate against its concentration gradient through co-transport with Na^+, H^+, and K^+ [2]. Astrocytes compensate for associated changes in membrane potential and pH through ion channel systems (particularly KIR4.1) and exchangers, as well as through the ability to dissipate ionic changes throughout the astrocytic network via connexin-dependent gap junctions [2].

Once captured, glutamate can enter several metabolic pathways within astrocytes. One of them is its conversion to α-ketoglutarate via the action of glutamate dehydrogenase or transaminase, followed by entry into the Krebs cycle [2]. Another key pathway is the transformation of glutamate into the non-toxic glutamine via the enzyme glutamine synthetase. Glutamine is transported back into the extracellular space using the Na^+-dependent transporter SNAT3 and enters neurons, where phosphate-activated glutaminase converts it back to glutamate [2]. Thus, the glutamate-glutamine cycle occurs, which is considered a key mechanism for maintaining the balance of excitatory transmission and neuronal metabolism.

Impairment of the function or expression of glutamate transporters, especially EAAT1 and EAAT2, leads to elevated extracellular glutamate levels, promoting the development of excitotoxicity, neuroinflammation, and oxidative stress [2, 34].

In this case, the excessive amount of glutamate not only fails to be cleared from the synaptic cleft but can also be released into the extracellular space, activating ionotropic (NMDA, AMPA, kainate) and metabotropic receptors on the surface of neurons [2, 45, 46]. Activation of NMDA receptors is particularly dangerous, leading to massive Ca^{2+} influx into the cell and initiating the so-called "excitotoxicity" cascade [2, 45, 46]. This process is accompanied by the activation of calcium-dependent enzymes (NO synthase, phospholipases, caspases), contributing to oxidative stress, disruption of cell membrane structure, and mitochondrial dysfunction. As noted by Todd and Hardingham, "If glutamate escapes the synaptic region, it can activate extrasynaptic NMDA receptors: excessive Ca^{2+} influx through these extrasynaptic NMDA receptors induces signaling cascades that initiate cell death programs" [46].

Inflammatory process and microglial activation. "In the 'resting' state, microglia vigorously infiltrate the local microenvironment, extending and retracting motile processes equipped with a vast number of surface receptors. Detection of any specific or nonspecific stimuli related to infection or tissue damage stimulates microglia to perform an appropriate response" [47]. In response to infectious or damaging signals, microglia transition to a reactive state, changing both morphology and functional activity [47]. Activated microglia phenotypes are traditionally divided into M1 (pro-inflammatory, neurotoxic) and M2 (anti-inflammatory, neuroprotective), although modern transcriptomic and proteomic studies show that such classification is conditional, as in vivo microglia display a wide spectrum of mixed functional states [47]. M1-like microglia produce pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), chemokines, eicosanoids, and reactive oxygen/nitrogen species; this, in turn, leads to further damage to neurons and astrocytes [47]. M2-like microglia, on the contrary, promote inflammation resolution and tissue repair by producing anti-inflammatory mediators and enzymes, including arginase [47]. Histochemically, activated microglia are characterized by elevated expression of specific markers such as CD68, Iba1, and major histocompatibility complex class II (MHC II), which is used as an indicator of the cell's immunological activity [48]. The release of pro-inflammatory cytokines, particularly IL-1β, TNF-α, and IL-6, in this context exacerbates damage to surrounding neurons and astrocytes, creating a pathological cycle of inflammation [47, 48].

Clinical manifestations of acetonemic syndrome and hyperammonemia. The clinical consequences of acetonemic syndrome and hyperammonemia are closely associated with the neurotoxic effects of metabolic disturbances affecting the functioning of the central nervous system in children [49]. Common manifestations include seizure syndrome, transient or prolonged consciousness disturbances (ranging from stupor to coma), coordination disorders, irritability or conversely lethargy, as well as cognitive impairments—such as delays in speech, language and psychomotor development [49].

Pathophysiologically, these symptoms are caused by the action of elevated concentrations of ketone bodies and ammonia on brain tissue [50–51]. The presence of ketone bodies exacerbates this effect by lowering pH in brain tissues and impairing the function of neuroglial structures. This contributes to impaired synaptic transmission, reduced activity of the GABAergic (inhibitory) system, and, consequently, the development of seizure syndrome [50–51]. The obtained data are shown schematically in ***Fig. 1***.

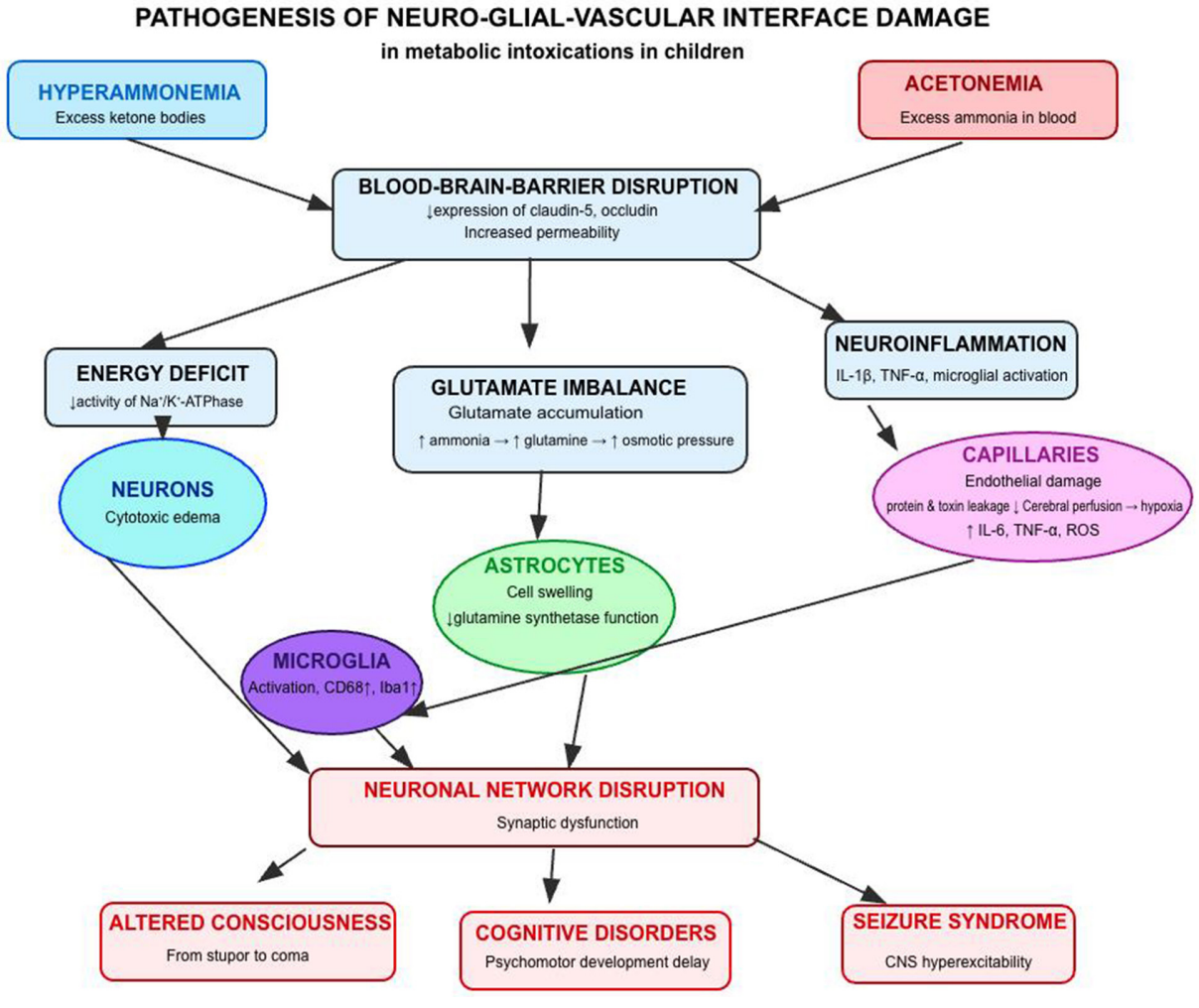

Fig. 1. Pathogenesis of neuro-glial-vascular interface damage in metabolic intoxications in children

Morphofunctional changes in the central nervous system. At the morphofunctional level, histologically, swelling of astrocytes, perivascular infiltrates, neuronal destruction, and activated microglia can be observed. Lesions predominantly affect subcortical structures, cerebral cortex, hippocampus, and cerebellum — areas most sensitive to hypoxia and metabolic imbalance [52-55].

Therapeutic aspects of managing pediatric patients with disturbances of the neuro-glial-vascular interface in metabolic intoxications, particularly in acetonemic syndrome and hyperammonemia, should be multi-step and include comprehensive treatment aimed at eliminating toxic metabolites, restoring water-electrolyte balance, as well as stabilizing structural and functional disorders caused by the effects of toxins on the neuro-glial-vascular interface.

In cases of severe hypoglycemia, intravenous administration of glucose is indicated to restore its normal level in the blood [56]. One of the most important aspects of treatment is the correction of elevated ammonia levels in hyperammonemia and ketone bodies in acetonemic syndrome.

For hyperammonemia, pharmacological agents such as L-arginine or sodium benzoate are used to help reduce ammonia levels, which have a toxic effect on the nervous system. Treatment begins with an initial dose and continues as maintenance therapy depending on the patient's age and weight. L-arginine can be prescribed at a dose of 250–400 mg/kg (maximum 12 g) for children up to 20 kg, and for children over 20 kg — 250 mg/kg up to 12 g per day [56].

Sodium benzoate and sodium phenylacetate are used to improve detoxification. For children up to 20 kg, the dosage is 250 mg/kg; for children over 20 kg, the dosage is 5.5 g/m² per day, not exceeding 12 g/day [56].

Other drugs used to correct disturbances related to hyperammonemia include carnitine, which promotes the removal of toxic metabolic products. It is administered at an initial dose of 50 mg/kg followed by a maintenance dose of 100 mg/kg per day divided into 4 doses [56]. Coenzyme therapy, including biotin and hydroxocobalamin, is also applied to help normalize metabolic processes in the body [56]. To reduce levels of toxic metabolites, particularly ammonia, osmotic laxatives (polyethylene glycol) and antibacterial drugs such as rifaximin are recommended [56].

Successful management of patients with acetonemic syndrome and hyperammonemia requires continuous monitoring of ammonia levels, ketone bodies, electrolytes, and other biochemical parameters [56].

Treatment must be individualized, with dosage adjustments and selection of therapeutic measures depending on the dynamics of the patient's clinical condition. Comorbidities, as well as the age and other individual characteristics of children, should also be taken into account. Since the diseases may be accompanied not only by physical but also psychological changes, it is important to provide psychological support for both patients and their families. This is especially relevant for children who may be frightened by frequent hospitalizations, pain, and the need for prolonged treatment.

Moreover, attention should be paid to preventing relapses through dietary and lifestyle correction, especially in children with a burdened hereditary background or predisposition to metabolic disorders.

Conclusions

Morphofunctional changes of the neuro-glial-vascular interface in acetonemic syndrome and hyperammonemia in children are associated with disruptions of the BBB structure, manifested by decreased expression of tight junction proteins such as claudin-5, occludin, and ZO-1. This is accompanied by cytotoxic astrocyte swelling, disorganization of astrocytic endfeet, and disturbed aquaporin expression. The main mechanisms of central nervous system injury are energy imbalance due to impaired glycolysis and mitochondrial dysfunction, disruption of sodium-potassium pumps leading to depolarization of cell membranes, as well as dysregulation of neurotransmitter balance, particularly excessive glutamate accumulation causing excitotoxicity. An important aspect is microglial activation with increased expression of CD68, Iba1, MHC II, and secretion of proinflammatory cytokines.

For the early diagnosis of neurotoxic complications, comprehensive monitoring of biomarkers such as S100β, NSE, GFAP for BBB damage, as well as IL-1β, TNF-α for neuroinflammation and indicators of neuronal dysfunction in serum and cerebrospinal fluid is necessary. Personalized therapy should consider different mechanisms of injury, including the use of membrane stabilizers for BBB damage, energotropic drugs to correct energy metabolism disturbances, and modulators of glutamatergic transmission for treating excitotoxicity. A multidisciplinary approach—aimed at early detection and correction of cognitive and behavioral disorders, as well as individualized neurorehabilitation programs considering age-related neuroplasticity features — is essential.

To improve diagnosis and treatment, educational programs for pediatricians and family doctors should be developed to facilitate in early diagnosis of neuro-glial-vascular interface disorders. Additionally, studies of potential neuroprotective agents that can stabilize astrocyte-endothelial interactions should be conducted, as well as preventive strategies developed for children with hereditary predisposition to metabolic disorders. Establishing a national patient registry would enable the study of long-term outcomes and evaluation of the effectiveness of various therapeutic approaches, improving the diagnosis and management of pediatric metabolic intoxications.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

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