Review

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Hyperhomocysteinemia syndrome in children with various diseases

Nina V. Evdokimova[1], Lilia S. Lebedeva[2], Juilya A. Demchuk[1], Mariya S. Ilchenko[1], Olga B. Astafieva[1, 3]

[1] Saint Petersburg State Pediatric Medical University, 2 Litovskaya str., Saint Petersburg, 194100, Russian Federation

[2] I.I. Dedov National Medical Research Center of Endocrinology, 11 Dmitry Ulyanov str., Moscow, 117036, Russian Federation

[3] City Polyclinic No. 51, Children's Polyclinic Department No. 39, 54 Kosmonavtov ave., 196233, Saint Petersburg, Russian Federation

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ABSTRACT. ***Introduction.*** The problem of the relationship of homocysteine level with the development of pathological conditions is becoming more and more relevant every year. The article presents a literature review of works devoted to the study of this issue. ***Aim*** – to study the role of homocysteine in the development of various diseases in children using literary sources. ***Materials and methods.*** Using keywords (homocysteine, hyperhomocysteinemia, adolescents, children) we searched for papers published from 1969 to 2025 in PubMed, World Wide Science and eLIBRARY databases. 1200 studies were found, and 42 were selected for review, including 5 systematic reviews and meta-analyses. ***Results.*** Hyperhomocysteinemia initiates activation of the unified cellular-humoral defense system of the organism, manifested in the development of hypercoagulation, increase in the number of leukocyte-platelet coaggregates, increase in the level of autoantibodies, cytokines, adhesion molecules, change in the phenotype of lymphocytes, which has a damaging effect on organs and systems, causing their damage. ***Conclusions.*** Domestic and foreign studies of homocysteine, in healthy and sick children show the association of homocysteine, with various pathologies in children and adolescents. First of all, they confirm the significance of this indicator as a diagnostic biomarker. Further in-depth and large-scale study of this issue is necessary.

KEYWORDS: *homocysteine, hyperhomocysteinemia, adolescents*

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✉ *Nina V. Evdokimova*. E-mail: posohova.nina2014@yandex.ru

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Синдром гипергомоцистеинемии у детей при различных заболеваниях

Нина Викторовна Евдокимова[1], Лилия Сергеевна Лебедева[2], Юлия Аркадьевна Демчук[1], Мария Сергеевна Ильченко[1], Ольга Борисовна Астафьева[1, 3]

[1] Санкт-Петербургский государственный педиатрический медицинский университет, 194100, г. Санкт-Петербург, ул. Литовская, д. 2, Российская Федерация

[2] Национальный медицинский исследовательский центр эндокринологии им. И.И. Дедова, 117036, г. Москва, ул. Дмитрия Ульянова, д. 11, Российская Федерация

[3] Городская поликлиника № 51, детское поликлиническое отделение № 39, 196233, г Санкт-Петербург, пр. Космонавтов, д. 54, Российская Федерация

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РЕЗЮМЕ. ***Введение.*** Проблема взаимосвязи уровня гомоцистеина с развитием патологических состояний с каждым годом становится все более актуальной. В статье представлен литературный обзор работ, посвященных изучению данного вопроса. ***Цель*** — используя литературные источники, изучить роль гомоцистеина в развитии различных заболеваний у детей. ***Материалы и методы.*** Благодаря использованию ключевых слов (гомоцистеин, гипергомоцистеинемия, дети) был проведен поиск работ, опубликованных с 1969 по 2025 год в базах данных PubMed, World Wide Science и eLIBRARY. Найдено 1200 исследований, отобрано для обзора 42, в том числе 5 систематических обзоров и метаанализов. ***Результаты.*** Гипергомоцистеинемия инициирует активацию единой клеточно-гуморальной системы защиты организма, проявляющуюся в развитии гиперкоагуляции, росте числа лейкоцитарно-тромбоцитарных коагрегатов, увеличении уровня аутоантител, цитокинов, молекул адгезии, изменении фенотипа лимфоцитов, что оказывает повреждающее действие на органы и системы. ***Выводы.*** Отечественные и зарубежные исследования гомоцистеина у здоровых и больных детей показывают связь гипергомоцистеинемии с различными патологиями у детей и подростков. В первую очередь, они подтверждают значимость этого показателя как диагностического биомаркера. Необходимо дальнейшее углубленное и масштабное изучение данного вопроса.

КЛЮЧЕВЫЕ СЛОВА: *гомоцистеин, гипергомоцистеинемия, подростки*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

✉ *Нина Викторовна Евдокимова*. E-mail: posohova.nina2014@yandex.ru

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INTRODUCTION

In recent years, the correlation between elevated plasma homocysteine (Hcy) concentrations and the development of a range of childhood disorders has attracted considerable research attention in the fields of pediatrics and biochemistry. Published epidemiological data indicate that homocysteine levels exceeding 15 μmol/L — a condition referred to as hyperhomocysteinemia (HHCy) — are found in approximately 5–7% of the general population [1–6].

More than half a century ago, Kilmer S. McCully proposed the hypothesis that elevated Hcy concentrations exert pathogenic effects on the human body. This supposition was grounded in clinical observations of children with inborn errors of methionine metabolism. In these patients, HHCy was accompanied by severe cardiovascular damage. In the absence of treatment, the disease typically had a fatal outcome: the children died at a young age from myocardial infarction or stroke. Postmortem examination consistently revealed the presence of atherosclerotic plaques in muscular arteries [1].

The development of HHCy is attributable to several factors. These include a metabolic factor — the level and activity of enzymes responsible for Hcy metabolism; the functional state of the kidneys, which governs homocysteine elimination; and a deficiency of vitamins B_6, B_{12}, and folic acid, which serve as cofactors (B_6, B_{12}) or substrates (folic acid). Early manifestation of HHCy is of particular interest, as it is associated in most cases with inherited defects in the genes encoding enzymes of the methylation and transsulfuration cycles [7, 8].

The universality of homocysteine's cytotoxic effects on cellular structures throughout the body is beyond dispute [9–15]. In this context, HHCy is gaining recognition as a potential risk marker for the onset and exacerbation of a broad spectrum of childhood diseases. Nevertheless, the pathogenetic role of this metabolic disturbance in pediatric practice remains controversial and warrants more detailed investigation.

The present review aims to systematize current evidence regarding the involvement of HHCy in the pathogenesis of various nosological entities in pediatric patients.

AIM

This review aims to evaluate the role of HHCy in the pathogenesis of various pediatric diseases.

MATERIALS AND METHODS

A search of PubMed, WorldWideScience, and eLIBRARY was conducted for studies published between 1969 and 2025 using the keywords "homocysteine," "hyperhomocysteinemia," and "children."

HOMOCYSTEINE: PHYSIOLOGICAL ROLE AND PLASMA CONCENTRATIONS IN CHILDREN

Homocysteine is a non-proteinogenic sulfhydryl amino acid synthesized endogenously via the intracellular demethylation of methionine; it is not obtained from dietary sources. Intracellular Hcy metabolism proceeds through two principal pathways: remethylation, regenerating methionine, and transsulfuration, producing cysteine. Remethylation represents the predominant cycle, its key cofactors being folate derivatives and cobalamin (vitamin B_{12}). The irreversible conversion of Hcy to cysteine takes place via the transsulfuration reaction, catalyzed by pyridoxal phosphate-dependent enzymes (Fig. 1) [16–19].

The physiological role of Hcy lies in maintaining stable methionine concentrations required for methylation reactions, as well as for the biosynthesis of cysteine — a structural component of glutathione and a source of sulfides. Additionally, Hcy participates in the synthesis of α-ketobutyrate, the immediate precursor of succinyl-CoA, an intermediate of the Krebs cycle [20].

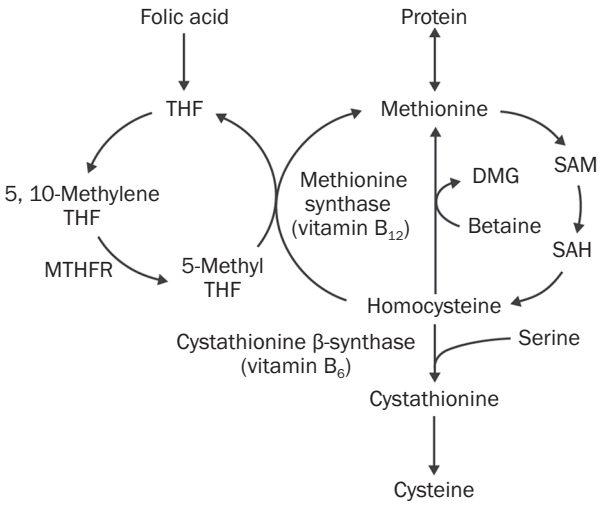

Fig. 1. Homocysteine metabolism [20]

Рис. 1. Метаболизм гомоцистеина [20]

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Fasting plasma homocysteine is generally considered normal within the range of 5 to 15 μmol/L. In children and adolescents, levels approximate 5 μmol/L; over the lifespan, mean Hcy concentrations increase by 3–5 μmol/L and are consistently higher in males than in females. Age-dependent changes are attributable to declining renal function, whereas higher baseline values in males reflect greater muscle mass. Plasma homocysteine concentrations of 15–30 μmol/L define moderate hyperhomocysteinemia, 30–100 μmol/L intermediate hyperhomocysteinemia, and >100 μmol/L severe hyperhomocysteinemia [21–25].

HYPERHOMOCYSTEINEMIA AND CARDIOVASCULAR DISEASE

A growing body of evidence identifies homocysteine (Hcy) as a significant contributor to cardiovascular pathology in children and adolescents. The pathogenesis is mediated by several interrelated mechanisms. The first is downregulation of adenosine receptors and upregulation of proinflammatory cytokines, which jointly impair myocardial perfusion. The second is oxidative stress resulting from the accumulation of reactive oxygen species. The third is elevated levels of asymmetric dimethylarginine — an endogenous inhibitor of nitric oxide synthase, a pivotal mediator of vasodilation. The combined influence of elevated Hcy and its metabolites on the vascular wall promotes endothelial dysfunction and vascular remodeling, thus establishing a substrate for the early onset of arterial hypertension in childhood. Of particular concern is the proatherosclerotic potential of HHCy, which may be amplified by genetic variants (polymorphisms) in genes encoding key enzymes of the folate cycle, including *MTHFR*, *MTRR*, and *MTR*. Collectively, these observations argue for the implementation of rigorous screening and preventive measures in patients with documented hyperhomocysteinemia [26–29].

HYPERHOMOCYSTEINEMIA AND OBESITY

To date, original studies that could definitively establish the relationship between these two pathologies remain limited. Nevertheless, available data point to an association between elevated homocysteine concentrations and an increased risk of cardiovascular complications in children with obesity relative to their normal-weight peers. A study conducted at Kemerovo Medical University included 81 adolescents, 65 of whom had a body mass index (BMI) above the 95th percentile. The results demonstrated that structural myocardial changes were detected 2.2 times more frequently in patients with a BMI above the 95th percentile and hyperhomocysteinemia exceeding 210 μmol/L than in children with normal Hcy levels. The risk of cardiac remodeling was statistically significantly higher in children with hyperhomocysteinemia [30–32].

HYPERHOMOCYSTEINEMIA AND UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA SYNDROME

Undifferentiated connective tissue dysplasia (UCTD) is a genetically determined condition characterized by defects in the fibrous structures and ground substance of connective tissue, resulting in multiorgan damage that shapes the profile of associated comorbidities and drug responses. Studies investigating the link between hyperhomocysteinemia and UCTD in children and adolescents are scarce. Yu.I. Rovda et al. examined 210 children aged 1 to 17 years, 58 of whom carried a clinically established diagnosis of UCTD. The aim of the study was to determine Hcy levels in patients with HHCy. The authors found that homocysteine levels were elevated both in patients with UCTD and in healthy children. However, the majority of patients with UCTD and HHCy reported an increased bleeding tendency, which may point to an association between hemorrhagic syndrome and homocysteine levels. A direct correlation was also observed between blood homocysteine levels and von Willebrand factor. This finding suggests a greater damaging effect of homocysteine on the endothelium in patients with UCTD, which may predispose to earlier development of thrombotic complications [33].

HYPERHOMOCYSTEINEMIA AND MIGRAINE

Several published studies point to an association between elevated homocysteine concentrations and migraine in children. From a pathogenetic standpoint, endothelial dysfunction occurring in the context of HHCy contributes to the development of this pathology. Elevated blood homocysteine promotes the accumulation of proinflammatory cytokines, including IL-6, IL-8, and TNF-α, increases reactive oxygen species, and diminishes vasodilatory components. Collectively, these effects play an important role in the cerebrovascular regulation of

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migraine, and intracranial arterial vasoconstriction may intensify pain. A neurogenic theory has also been advanced, according to which the release of neurotransmitters from trigeminal nerve neurons triggers marked vasodilation and edema. In genetically determined HHCy due to the *C677T* mutation in the gene, migraine attacks are provoked by the excessive accumulation of excitotoxic amino acids exerting a direct toxic effect on the brain. Elevated blood Hcy has been documented in children with migraine in several studies. These observations warrant consideration both in patients with newly diagnosed migraine — to address all components of pathogenesis — and in individuals with HHCy, to prevent the development of migraine [34–36].

HYPERHOMOCYSTEINEMIA AND DISEASES OF THE URINARY SYSTEM

The kidneys play a well-established central role in homocysteine metabolism, as the greater part of Hcy undergoes a series of metabolic transformations within the renal tubules. Accordingly, when Hcy levels rise, the kidneys are the first organs to sustain damage. O.V. Nesterenko et al. demonstrated that in children with chronic pyelonephritis, the development of nephrosclerosis was associated with elevated blood homocysteine. Patients with this diagnosis should therefore be regarded as being at risk for nephrosclerosis. Moreover, the detection of HHCy in a patient with renal disease may provide a rationale for initiating homocysteine-lowering therapy [36, 37].

HYPERHOMOCYSTEINEMIA AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The interrelationship between HHCy and the renin-angiotensin-aldosterone system (RAAS) continues to be debated. Nevertheless, given the established role of hyperhomocysteinemia in promoting arterial hypertension and renal pathology, it is reasonable to hypothesize that HHCy may adversely affect the RAAS and thereby further drive the development of arterial hypertension, including in children [38].

HYPERHOMOCYSTEINEMIA AND NEUROINFECTIONS

Neuroinfections remain a significant clinical challenge across multiple medical disciplines due to the high risk of severe complications. The outcome of infectious central nervous system involvement depends on a constellation of factors, most notably the magnitude of the inflammatory response and the functional integrity of the vascular endothelium. Plasma homocysteine concentration is recognized as an important laboratory marker of endothelial dysfunction. T.S. Berezovskaya and N.A. Mironova analyzed blood samples from 60 patients, 30 of whom formed a group with neuroinfections of diverse etiology and severity. Their findings revealed a statistically significant elevation of Hcy levels in patients with neuroinfections — an elevation that was universal in character and independent of the specific pathogen [19, 39–42].

HYPERHOMOCYSTEINEMIA AND THE DEVELOPMENT OF NEUROLOGICAL DISORDERS

S. Yoganathan et al. and B. Li et al. have reported clinical cases in which HHCy presented with a spectrum of neurological manifestations, including epileptic seizures, autism spectrum disorder, hyporeflexia, atonia, and encephalopathy. In each of these cases, screening of blood homocysteine and methionine levels was undertaken, and disturbances in the metabolism of this amino acid were confirmed in all instances. The initiation of appropriate pharmacological therapy aimed at reducing blood homocysteine was followed by clinical improvement [22, 30, 31, 37, 40].

CONCLUSION

Hyperhomocysteinemia sets in motion a complex cellular and humoral defense response. The clinical and laboratory hallmarks of this process include the development of hypercoagulation, an increase in leukocyte-platelet aggregates, and rising concentrations of autoantibodies, proinflammatory cytokines, and adhesion molecules. Alterations in the phenotypic profile of leukocytes are also observed. Together, these factors drive endothelial dysfunction and tissue injury [26, 39].

Studies of Hcy in healthy children and those with various diseases, conducted both nationally and internationally, point to an association between HHCy and a range of pediatric and adolescent pathologies. Importantly, they affirm the value of this parameter as a diagnostic biomarker. Further in-depth, large-scale investigation of this subject is warranted.

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ADDITIONAL INFORMATION

Authors' contribution. Concept of the article — N.V. Evdokimova, L.S. Lebedeva, J.A. Demchuk, M.S. Ilchenko, O.B. Astafieva; text development — N.V. Evdokimova, L.S. Lebedeva, J.A. Demchuk, M.S. Ilchenko, O.B. Astafieva; editing — N.V. Evdokimova, L.S. Lebedeva; approval of the final version of the article — N.V. Evdokimova.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Authors' info

✉ **Nina V. Evdokimova** — Cand. Sci. (Med.), Assistant, Department of propaedeutics of pediatric diseases with a course of general pediatric care.
E-mail: posohova.nina2014@yandex.ru;
https://orcid.org/0000-0001-9812-6899; SPIN: 6552-7359
Lilia S. Lebedeva — Pediatric Endocrinologist-Resident.
E-mail: ms.liliya063@gmail.com;
https://orcid.org/0009-0002-7799-0754; SPIN: 8913-5966
Juilya A. Demchuk — Pediatric Endocrinologist of the clinics, Head of the Endocrinology Department.
E-mail: julia.demchuk.a@gmail.com;
https://orcid.org/0000-0002-0851-2794
Maria S. Ilchenko — Assistant Professor, Department of Propaedeutics of Childhood Diseases with a course in general child care, Pediatric Endocrinologis of the clinics.
E-mail: mariya-mimiple@mail.ru;
https://orcid.org/0009-0009-0513-2954; SPIN: 6243-6447
Olga B. Astafieva — Assistant Professor, Department of Propaedeutics of Childhood Diseases with a course in general child care, Saint Petersburg State Pediatric Medical University; Pediatrician City Polyclinic No. 51, Children's Polyclinic Department No. 39.
E-mail: bolek55@yandex.ru

Об авторах

✉ **Нина Викторовна Евдокимова** — к.м.н., ассистент, кафедра пропедевтики детских болезней с курсом общего ухода за детьми. E-mail: posohova.nina2014@yandex.ru;
https://orcid.org/0000-0001-9812-6899; SPIN: 6552-7359

Лилия Сергеевна Лебедева — врач-ординатор, детский эндокринолог. E-mail: ms.liliya063@gmail.com;
https://orcid.org/0009-0002-7799-0754; SPIN: 8913-5966
Юлия Аркадьевна Демчук — врач детский эндокринолог клиники, заведующий структурным подразделением эдокринологического отделения. E-mail: julia.demchuk.a@gmail.com;
https://orcid.org/0000-0002-0851-2794
Мария Сергеевна Ильченко — ассистент, кафедра пропедевтики детских болезней с курсом общего ухода за детьми, врач детский эндокринолог клиники.
E-mail: mariya-mimiple@mail.ru;
https://orcid.org/0009-0009-0513-2954; SPIN: 6243-6447
Ольга Борисовна Астафьева — ассистент, кафедра пропедевтики детских болезней с курсом общего ухода за детьми, Санкт-Петербургский государственный педиатрический медицинский университет; врач-педиатр, городская поликлиника № 51, детское поликлиническое отделение № 39.
E-mail: bolek55@yandex.ru

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