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# COGNITIVE IMPAIRMENT IN ANEMIAS OF VARIOUS GENESIS: METABOLIC AND VASCULAR MECHANISMS. LITERATURE REVIEW

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**ABSTRACT.** Anemia, one of the most common hematological syndromes globally, is traditionally associated with clinical manifestations such as weakness, fatigue, and shortness of breath. However, compelling data accumulated in recent decades indicate a significant impact of anemias of various origins on cognitive functions. The aim of this literature review is to systematically analyze and synthesize current knowledge on the metabolic and vascular mechanisms underlying cognitive deficits in Iron Deficiency Anemia (IDA), B12 Deficiency Anemia, and Anemia of Chronic Disease (ACD). An analysis of over 50 scientific sources demonstrates that hypoxia, resulting from reduced blood oxygen-carrying capacity, is a universal but not the sole pathogenetic factor. Metabolic mechanisms include impaired synthesis of neurotransmitters (dopamine, norepinephrine), myelination of nerve fibers (in B12 and iron deficiency), mitochondrial dysfunction, and oxidative stress. Vascular mechanisms are related to compensatory cerebral vasodilation, impaired autoregulation of cerebral blood flow, endothelial dysfunction, and accelerated cerebral small vessel disease. The results section presents integrated pathogenetic pathways and a comparative analysis of the features of cognitive deficits depending on the anemia's genesis. It is established that cognitive impairments in anemia are often reversible in the early stages, underscoring the importance of timely diagnosis and pathogenetic therapy. It is concluded that a comprehensive consideration of metabolic and vascular components is necessary for developing effective neuroprotection strategies for patients with anemia.

**Keywords:** Anemia, Cognitive Functions, Iron Deficiency Anemia, B12 Deficiency Anemia, Anemia of Chronic Disease, Hypoxia, Cerebral Blood Flow, Neurotransmitters, Myelin, Oxidative Stress, Endothelial Dysfunction, Hippocampus, Prefrontal Cortex.

# РАСПРОСТРАНЕННОСТЬ СИМПТОМОВ ИММУНОДЕФИЦИТА В ГРУППАХ НАСЕЛЕНИЯ С ГИМЕНОЛЕПИДОЗОМ

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**АННОТАЦИЯ.** Анемия, один из наиболее распространенных гематологических синдромов в мире, традиционно ассоциируется с такими клиническими проявлениями, как слабость, утомляемость и одышка. Однако убедительные данные, накопленные за последние десятилетия,

свидетельствуют о значительном влиянии анемий различного происхождения на когнитивные функции. Целью данного обзора литературы является систематический анализ и обобщение современных знаний о метаболических и сосудистых механизмах, лежащих в основе когнитивного дефицита при железодефицитной анемии (ЖДА), В12-дефицитной анемии и анемии хронических заболеваний (АХЗ). Анализ более 50 научных источников показывает, что гипоксия, возникающая в результате снижения кислородтранспортной способности крови, является универсальным, но не единственным патогенетическим фактором. Метаболические механизмы включают нарушение синтеза нейромедиаторов (дофамина, норадреналина), миелинизации нервных волокон (при дефиците В12 и железа), дисфункцию митохондрий и оксидативный стресс. Сосудистые механизмы связаны с компенсаторной вазодилатацией сосудов головного мозга, нарушением ауторегуляции мозгового кровотока, эндотелиальной дисфункцией и ускоренным развитием церебральной микроангиопатии. В разделе результаты представлены интегрированные патогенетические пути и сравнительный анализ особенностей когнитивных нарушений в зависимости от генеза анемии. Установлено, что когнитивные нарушения при анемии часто обратимы на ранних стадиях, что подчеркивает важность своевременной диагностики и патогенетической терапии. Сделан вывод о том, что комплексный учет метаболических и сосудистых компонентов необходим для разработки эффективных стратегий нейропротекции у пациентов с анемией.

**Ключевые слова:** Анемия, Когнитивные функции, Железодефицитная анемия, В12-дефицитная анемия, Анемия хронических заболеваний, Гипоксия, Церебральный кровоток, Нейромедиаторы, Миелин, Окислительный стресс, Эндотелиальная дисфункция, Гиппокамп, Префронтальная кора.

**Introduction.** Anemia represents a global health problem, affecting approximately a quarter of the world's population, with the highest prevalence among children, pregnant women, and the elderly [WHO, 2021]. Historically, the focus of clinical and research efforts has been on the systemic manifestations of anemia, such as reduced exercise tolerance, cardiovascular complications, and diminished quality of life. However, a growing body of epidemiological and clinical research indicates a consistent association between anemia and impairments in the cognitive domain, including deficits in attention, memory, executive functions, and information processing speed [Lukowski et al., 2010; Andro et al., 2013].

The classic and most obvious explanation is cerebral hypoxia resulting from reduced blood oxygen capacity. However, hypoxia alone cannot fully explain the entire spectrum of cognitive disorders and their specificity in different types of anemia. For instance, in Iron Deficiency Anemia, the key role is played by iron's involvement in catecholamine metabolism and myelogenesis [Beard, 2001], whereas in B12 Deficiency Anemia, demyelination and accumulation of

neurotoxic metabolites dominate [Green et al., 2017]. In Anemia of Chronic Disease, pro-inflammatory cytokines independently disrupt neuroplasticity and the function of the blood-brain barrier [Simmons, 2022].

The purpose of this literature review is to conduct a comprehensive analysis and synthesis of current data on the metabolic and vascular mechanisms of cognitive impairment in anemias of various genesis. The objectives of this work are:

1. To analyze the role of the universal factor of hypoxia.
2. To identify specific metabolic disturbances for IDA, B12 Deficiency Anemia, and ACD.
3. To assess the contribution of vascular mechanisms, including changes in cerebral hemodynamics and endothelial dysfunction.
4. To conduct a comparative characterization of the cognitive profile in various anemias.
5. To visualize complex pathogenetic pathways and discuss promising therapeutic directions.

**Literature review.** *1. Universal Mechanism: Cerebral Hypoxia and Energy Metabolism.* A decrease in hemoglobin concentration directly leads to reduced oxygen delivery to tissues, including the brain, which is one of the most metabolically active and oxygen-dependent organs. Compensatory increases in cerebral blood flow (CBF) are confirmed by functional MRI and transcranial Doppler ultrasonography data [Ivanov et al., 2019]. However, the capacity for this compensation is limited. In severe anemia, the mechanisms of cerebral blood flow autoregulation can be impaired, leading to relative ischemia in the most vulnerable areas, such as the hippocampus and frontal lobes [Osipova, 2020].

Hypoxia induces the expression of HIF-1α (Hypoxia-Inducible Factor 1-alpha), which regulates a wide range of adaptive genes. Although short-term HIF-1α activation may have a protective effect, chronic hypoxia leads to disruption of energy metabolism: the efficiency of oxidative phosphorylation in neuronal mitochondria decreases, ATP levels fall, and dependence on less efficient anaerobic glycolysis increases [Vasnetsov, 2018]. This directly affects processes requiring significant energy expenditure – maintaining the resting potential, synaptic transmission, and long-term potentiation, which is the cellular basis of memory.

*2. Specific Metabolic Mechanisms in Various Anemias.*

Iron is a cofactor for numerous key enzymes in the brain. Neurotransmitter Synthesis. Iron is a component of tyrosine hydroxylase, a key enzyme in the synthesis of dopamine and norepinephrine. Iron deficiency leads to decreased levels of these catecholamines in the striatum and prefrontal cortex, clinically manifesting as impairments in attention, executive functions, and motivation [Beard, 2001, p. 372]. "Dopaminergic pathways, particularly the mesocorticolimbic pathway, are critically dependent on adequate iron availability," emphasizes J. Beard in her review.

Myelinogenesis. Oligodendrocytes, responsible for myelin formation, require high iron content for the activity of lipid synthesis enzymes and energy production. IDA, especially during critical periods of development (infancy, early childhood), leads to hypomyelination and impaired nerve impulse conduction velocity [Lozoff, 2011, p. 55]. This may explain the persistent cognitive deficits that remain even after anemia correction.

Oxidative Stress. Paradoxically, iron deficiency can enhance oxidative stress in the brain. Iron is a component of catalase and other antioxidant enzymes. Its deficiency reduces antioxidant defense, making neurons more vulnerable to damage by reactive oxygen species [Sokolova, 2017].

Cobalamin (Vitamin B12) deficiency has a direct neurotoxic effect. Demyelination. Vitamin B12 is a cofactor in the synthesis of methionine from homocysteine. In its deficiency, homocysteine accumulates and the level of S-adenosylmethionine (SAM) decreases, which is a universal methyl group donor. This disrupts the methylation of myelin basic proteins and lipids, leading to myelin instability and demyelination, primarily in the spinal cord and brain [Green et al., 2017, p. 215].

Accumulation of Toxic Metabolites. Besides homocysteine, methylmalonic acid (MMA) accumulates in B12 deficiency. Both metabolites are neurotoxic, inducing neuronal apoptosis, disrupting mitochondrial function, and potentiating excitotoxicity through NMDA receptor activation [Mikhailov, 2020].

Impaired Neurotransmitter Synthesis. SAM is also necessary for the synthesis of catecholamines and serotonin. Thus, B12 deficiency indirectly affects neurotransmitter balance.

ACD develops against a background of chronic inflammation (oncological, rheumatic, infectious diseases). The pathogenesis of its cognitive impairments is unique.

Inflammatory Hypothesis. Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), which are elevated in ACD, cross the blood-brain barrier and exert a direct damaging effect on neurons and glial cells. They suppress neurogenesis in the hippocampus, impair synaptic plasticity, and induce apoptosis [Simmons, 2022, p. 104].

Iron Metabolism Dysfunction. In ACD, functional iron deficiency develops: macrophages sequester iron, making it unavailable for erythropoiesis. This process can also limit iron availability for neurons, secondarily triggering mechanisms similar to those in IDA, albeit in a less pronounced form.

Reduced Erythropoietin (EPO) Production. Inflammation suppresses renal EPO production. Beyond its hematopoietic function, EPO is a potent neuroprotective cytokine in the CNS. It has anti-inflammatory, anti-apoptotic properties and stimulates neurogenesis. Decreased EPO levels in ACD deprive the brain of an important protective factor [Smith, 2014].

*3. Vascular Mechanisms of Cognitive Impairment.*

Impaired Autoregulation of Cerebral Blood Flow. Prolonged compensatory vasodilation in anemia can deplete the vasomotor reserve of cerebral vessels. This

makes cerebral blood flow more dependent on systemic blood pressure, increasing the risk of both ischemia during hypotension and hyperperfusion injury during hypertension [Ivanov et al., 2019, p. 45].

Endothelial Dysfunction. Chronic hypoxia and concomitant inflammation (especially in ACD) damage the endothelium of cerebral vessels. The production of the vasodilator NO decreases, while the level of vasoconstrictors (endothelin-1) increases. This impairs microcirculation and contributes to the development of cerebral microangiopathy [Osipova, 2020].

Link to Cerebrovascular Pathology. Anemia has been identified as an independent risk factor for stroke and vascular cognitive impairment. Patients with anemia more frequently exhibit silent lacunar infarcts and leukoaraiosis on MRI, which directly correlates with the severity of cognitive deficit [Verdelho et al., 2010].

This section presents the results of systematizing literature data in the form of integrated pathogenetic pathways and comparative tables.

**Table 1.**

**Comparative Characteristics of Cognitive Impairments and Key Mechanisms in Anemias of Various Genesis.**

| Parameter | Iron Deficiency Anemia (IDA) | B12-Deficiency Anemia | Anemia of Chronic Disease (ACD) |
|---|---|---|---|
| **Predominant Cognitive Domains** | Executive functions, attention, processing speed. | Memory, processing speed, visuospatial functions, possible psychotic disorders. | Global cognitive decline, psychomotor slowing, memory deficit. |
| **Key Metabolic Mechanisms** | Dopamine/ norepinephrine deficiency, hypomyelination, oxidative stress. | Demyelination, accumulation of homocysteine and MMA, neurotoxicity. | Inflammatory cytokine-induced dysfunction, functional iron deficiency, reduced EPO. |
| **Key Vascular Mechanisms** | Impaired autoregulation, endothelial dysfunction. | Endothelial dysfunction (homocysteine-mediated), increased thrombosis risk. | Pronounced endothelial dysfunction, accelerated atherosclerosis and microangiopathy. |
| **Reversibility with Treatment** | High in early stages; may be incomplete with long-term childhood deficiency. | Depends on deficiency duration; neurological changes may be irreversible. | Partial; depends on successful therapy of the underlying inflammatory disease. |

Neuroimaging Data Visualization. Numerous studies using voxel-based morphometry (VBM) and diffusion-tensor imaging (DTI) demonstrate that patients with chronic anemia have reduced grey matter volume in the prefrontal cortex and hippocampus, as well as decreased fractional anisotropy (FA) in white matter, indicating impaired integrity of conductive pathways [Zhou et al., 2021]. These structural changes are the morphological substrate of the identified cognitive deficit.

One of the key discussion points is the issue of the reversibility of cognitive deficits. Evidence suggests that the earlier pathogenetic therapy is initiated (iron supplementation, vitamin B12, inflammation control), the higher the likelihood of complete cognitive recovery [Lukowski et al., 2010; Green et al., 2017]. However, the concept of a "critical period" exists, particularly relevant for IDA in early childhood. Iron deficiency during the period of active brain development can lead to persistent, not fully reversible changes in neural network architecture, manifesting in later life periods [Lozoff, 2011, p. 58]. This underscores the importance of preventive screening programs.

**Conclusion.** This literature review demonstrates that cognitive impairment is an integral and clinically significant component of anemias of various genesis. The pathogenesis of these impairments is multicomponent and includes:

1. A universal hypoxic component, leading to energy deficit and impaired neuronal function.
2. Specific metabolic disturbances determined by the type of anemia: dysfunction of catecholaminergic systems and myelogenesis in IDA; demyelination and neurotoxicity in B12 deficiency; inflammatory damage and reduced neuroprotection in ACD.
3. Vascular mechanisms, manifesting as impaired autoregulation of cerebral blood flow, endothelial dysfunction, and accelerated cerebrovascular pathology.

The interaction of these mechanisms leads to structural and functional changes in key cognitive brain areas – the hippocampus, prefrontal cortex, and white matter. Cognitive impairments in anemia are often potentially reversible, making their early diagnosis and adequate pathogenetic therapy an important reserve for preserving cognitive health and quality of life in patients. Further research should focus on identifying biomarkers of early cognitive risk and developing comprehensive neuroprotective strategies for this category of patients.

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