New Day in Medicine
Новый День в Медицине
NDM

TIBBIYOTDA YANGI KUN

Ilmiy referativ, marifiy-ma'naviy jurnal

AVICENNA-MED.UZ

ISSN 2181-712X.
EiSSN 2181-2187

4 (54) 2023

www.bsmi.uz
https://newdaymedicine.com
E: ndmuz@mail.ru
Тел: +99890 8061882

ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал

УЧРЕДИТЕЛИ:

БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»

Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского является генеральным научно-практическим консультантом редакции

Журнал был включен в список журнальных изданий, рецензируемых Высшей Аттестационной Комиссией Республики Узбекистан (Протокол № 201/03 от 30.12.2013 г.)

4 (54)

2023

апрель

Received: 20.03.2023, Accepted: 25.03.2023, Published: 20.04.2023.

UDC 616.831-005.1

THE ROLE OF HOMOCYSTEINE IN THE DEVELOPMENT OF COGNITIVE IMPAIRMENT IN CHRONIC CEREBRAL ISCHEMIA AND THE PROBLEM OF HYPERHOMOCYSTEINEMIA *(Literature review)*

Khaydarova Dildora Kadirovna[1]., Xatamova Sarvinoz Muyitdinovna[2]

[1] Tashkent Medical Academy 100109, Tashkent, Uzbekistan Farabi Street 2. Tel: +99878 1507825; E-mail: info@tma.uz
[2] Bukhara State Medical Institute named after Abu Ali ibn Sina Uzbekistan Bukhara, A.Navoi st. 1 Tel: +998(65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Resume***

Homocysteine is a sulfur-containing amino acid that is synthesized under physiological conditions from methionine. Normally, the concentration of homocysteine in the blood serum is 5 - 15 µmol /l. During life, the average level of homocysteine can increase by 3 - 5 µmol / l. A serum homocysteine level of more than 16 µmol /l significantly increases the risk of developing cardiovascular diseases. Hyperhomocysteinemia is a marker of kidney dysfunction and an independent risk factor for stroke. The article describes the role of homocysteine and the problem of hyperhomocysteinemia in the development of cognitive impairment in cerebrovascular diseases and chronic ischemic ischemia.

Keywords. Homocysteine, amino acid, hyperhomocysteinemia, cerebrovascular disease.

РОЛЬ ГОМОЦИСТЕИНА В РАЗВИТИИ КОГНИТИВНЫХ НАРУШЕНИЙ ПРИ ХРОНИЧЕСКОЙ ИШЕМИИ ГОЛОВНОГО МОЗГА, И ПРОБЛЕМА ГИПЕРГОМОЦИСТЕИНЕМИИ (*обзор литературы)*

Хайдарова Дилдора Кадировна[1]., Хатамова Сарвиноз Муйитдиновна[2]

[1]Ташкентская Медицинская Академия (TMA) Узбекистан, 100109, Ташкент, Алмазарский район, ул. Фароби, тел: +99878 1507825, E-mail: info@tma.uz
[2] Бухарский государственный медицинский институт имени Абу Али ибн Сины, Узбекистан, г. Бухара, ул. А. Навои. 1 Тел: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Резюме***

Гомоцистеин представляет собой серосодержащую аминокислоту, которая в физиологических условиях синтезируется из метионина. В норме концентрация гомоцистеина в сыворотке крови составляет 5 - 15 мкмоль/л. В течение жизни средний уровень гомоцистеина может увеличиваться на 3 - 5мкмоль/л. Сывороточный уровень гомоцистеина более 16 мкмоль/л достоверно повышает риск развития сердечно - сосудистых заболеваний. Гипергомоцистеинемия является маркером дисфункции почек и независимым фактором риска развития мозгового инсульта. В статье описывается роль гомоцистеина и проблема гипергомоцистеинемии в развитии когнитивных нарушений при цереброваскулярных заболеваниях и хронической ишемической ишемии.

Ключевые слова. Гомоцистеин, аминокислота, Гипергомоцистеинемия, цереброваскулярных заболевания.

SURUNKALI BOSHMIYA ISHEMIYASIDA KOGNITIV BUZILISHLARNING RIVOJLANISHIDA HOMOSISTEINNING ROLI VA GIPERHOMOSISTEINEMIYA MUAMMOSI *(Adabiyot sharhi)*

Xaydarova Dildora Kadirovna[1], Xatamova Sarvinoz Muyitdinovna[2]

[1] Toshkent tibbiyot akademiyasi, 100109 Toshkent, O‘zbekiston Tel: +998781507825 E-mail: info@tma.uz
[2] Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti, O‘zbekiston, Buxoro, st. A. Navoiy. 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Rezyume***

Gomosistein fiziologik sharoitda metionindan sintez qilinadigan oltingugurt o'zichiga olgan aminokislotadir. Odatda qon zardobida homosistein kontsentratsiyasi 5-15 mkmol/l ni tashkil qiladi. Hayot davomida homosisteinning o'rtacha darajasi 3-5 mkmol / l ga oshishi mumkin. Qon zardobidagi homosistein darajasi 16 mkmol / l dan yuqori bo'lsa, yurak-qon tomir kasalliklarini rivojlanish xavfini sezilarli darajada oshiradi. Giperhomosisteinemiya buyrak disfunktsiyasining belgisi va insult uchun mustaqil xavfomilidir. Maqolada serebrovaskulyar kasallik va Surunkali boshmiya ishemiyasida kognitiv buzilishlarning rivojlanishida homosisteinning roli va giperhomosisteinemiya muammosi tasvirlangan.

Kalit so'zlar. Homosistein, aminokislota, giperhomosisteinemiya, serebrovaskulyar kasallik.

Introduction

One of the basic directions for the prevention and treatment of cognitive impairment of various etiologies is the timely detection and correction of vascular risk factors. A significant factor leading to the development of cerebrovascular pathology and cognitive impairment is hyperhomocysteinemia , however, the existing data are rather contradictory. The level of homocysteine in blood plasma increases with age and is largely associated with the concentration of vitamins B12, B6, and folates [13].

In people of older age groups, moderate hyperhomocysteinemia (12–30 μmol /l) is found in 40% of cases [8]. Deficiency of folates, vitamins B_6 and B_{12}, renal failure and a certain polymorphism of the methylenetetrahydrofolate reductase gene are the most significant factors contributing to hyperhomocysteinemia. The main causes of vitamin deficiency are their insufficient intake with food (for example, with a vegetarian diet), malabsorption syndrome, or concomitant use of certain medications (metformin, omeprazole) [5]. Smoking causes a decrease in blood levels of vitamins Bb, B12 due to exposure to cyanides contained in cigarette smoke. Coffee consumption, alcohol abuse, chronic kidney dysfunction are also important [4].

C. Reitz, M.X. Tang, J. Miller [11] conducted a comparative assessment of the relationshipbetween homocysteine levels and the progression of cognitive impairment in two parallel groups. The first group included patients with an initially normal level of intellectual- mnestic functions, and the second group included patients with moderate cognitive impairment (MCI). The average follow-up period for patients was 5.2 years with an annual study of the level of homocysteine in blood plasma. Patients with MCI had higher levels of homocysteine in the blood plasma compared with the group of healthy individuals, however, the progression of disorders of higher cortical functions both in the MCI group and the appearance and progression of intellectualmnestic disorders in previously healthy individuals were not significantly accompanied by an increase in homocysteine.

The Rotterdam study observed an association between plasma homocysteine levels and neuropsychological outcomes. Lower values of the speed of thinking and short term verbal memory were observed in patients with plasma homocysteine levels of more than 14 μmol /L [10]. In an interim report from the Framingham study Offspring showed that cognitive impairment was related to plasma homocysteine levels in older adults among the elderly. In patients with initially higher levels of homocysteine, dementia developed significantly more often after several years, in contrast to patients with initially normal levels. In the NAME study, which studied the relationship between nutrition, age, and mnestic disorders in older people, higher concentrations of homocysteine were also found in patients with dementia [12].

In the Hordaland, study plasma homocysteine levels decreased in direct proportion to cognitive - ability over a 6-year follow-up period [9]. Approximately the same results were obtained in other multicenter studies: it was shown that homocysteine and its determinants (vitamin B12, folate) can affect cognitive impairment and the course of Alzheimer's disease (AD) [6]. Vitamin B deficiency and hyperhomocysteinemia are common in the elderly and are associated with the incidence of asthma [7]. The main mechanism for the development of dementia in hyperhomocysteinemia is the toxic effect of homocysteine on the vascular wall, which explains the development of cognitive disorders in cerebrovascular pathology. Thus, the progression of vascular or mixed dementia can be slowed down by taking folic acid, vitamin B_{12} and vitamin B_6 . In a recent placebo-controlled trial with vitamin support (folic acid 0.8 mg, B_{12} 0.5 mg, B_6 20 mg/day) for 24 months, Smith AD ef al. [15] observed a slowdown in the progression of cerebral atrophy according to magnetic resonance imaging. In patients

receiving therapy, the rate of atrophy was 29.6% slower. In another two-year placebo-controlled study in carotid stenosis, the use of 5 mg of folic acid and 250 mg of vitamin B_6 caused a slight, subtle improvement in hemodynamic parameters according to magnetic resonance angiography [16]. Patients who have had a stroke, in the presence of concomitant hyperhomocysteinemia, have more extensive ischemic damage to the medulla [4].

Recently, the range of studies begun in the 1990s [1] and devoted to the study of the role of neurotrophic factors in the formation of the fetal nervous system has been expanded. It has been established that such neurotrophins as the neurotrophic factor of the brain (brain-derived neurotrophic factor - BDNF) and nerve growth factor (nerve growth factor , NGF), are involved in the vital - processes of growth and differentiation of neurons in the central nervous system (CNS) and peripheral nervous system of the developing fetus [2–4]. It is most likely that the mechanism of action of these neurotrophic factors is related to their influence on angiogenesis and cell growth, survival, and maturation of neurons [2, 5].

Until recently, it was believed that the function of neurotrophins was limited by their influence on the development of the nervous system, but subsequently they began to be considered as compounds that mediate the connection between the immune, endocrine, and nervous systems during the perinatal period [4]. It has been established that the effects of neurotrophins are due to the presence of two types of transmembrane receptors: Trk receptors of the tropomyosin kinase family (TrkA, TrkB , TrkC) and p75 NTR belonging to the tumor necrosis factor receptor family . Receptors of the Trk family have a high affinity for certain mature neurotrophins: NGF predominantly binds to TrkA, while BDNF binds to the TrkB receptor [6]. The p75 ^{HTK} receptor has a low affinity for mature forms of neurotrophins , but at the same time, it binds their precursors proBDNF and proNGF with very high affinity , regulating the activation of various signaling pathways from cell growth and differentiation to cell death [7, 8].

Relatively recently, the role of neurotrophic factors in the development of the placenta has been established. In particular, the localization of neurotrophins and their Trk receptors both in trophoblasts and in decidual cells has been shown, which confirms the assumption that neurotrophins are involved in the process of implantation and development of the placenta, the formation of the uteroplacental and fetal-placental barriers [3, 9— 14]. In particular, it was shown that BDNF promotes cytotrophoblast differentiation and proliferation [10,11]; similar results were obtained for NGF [14]. It has been shown that BDNF mRNA expression in rat placenta increases with increasing gestational age and reaches its maximum by the 21st day of gestation [3]. The neurotrophic factors NGF, BDNF, and NT-3 have been suggested to play a significant role in the regulation of angiogenesis in the placenta, but the question remains how they affect the vascular endothelial growth factor (VEGF) and the activity of metalloproteinases (MMPs) in this process [15]. It is also important to emphasize that reciprocal effects occur between neurotrophic factors, in particular, NGF and VEGF. Thus, VEGF is involved not only in the processes of brain vascularization , but also in the proliferation of nerve cells [16]. Of particular importance is the study of the regulation of angiogenesis in the placenta with the participation of neurotrophic factors under conditions of hyperhomocysteinemia (HHC) in connection with the available data that an increased content of homocysteine can have a direct effect on the formation of placental vessels [17,18].

In the last decade, the attention of researchers , along with BDNF and NGF, has been attracted by the study of neuregulins that perform a neuroprotective function during the development of the fetal and newborn brain [19,20]. Separate works have appeared in which the expression of neuregulin 1 (NRG1) in the endothelium of the human umbilical cord [21] and in the maternal and fetal parts of the placenta of cows [22] has been established, which indicates the involvement of this neurotrophic factor in the relationship between mother and fetus organisms. The expression and secretion of neuregulin NRG1 by stromal decidual cells and its role in the paracrine regulation of survival, - differentiation, and provision of adequate invasion of cells of the extravillous trophoblast due to the activation of signaling pathways leading to suppression of apoptosis [23].

Many studies have confirmed that for the functioning of the processes of remethylation and transsulfonation, the body must have a sufficient content of vitamins B1 (riboflavin), B6 (pyridoxine), B12 (cyanocobalamin) and folic acid, which act as coenzymes [3,7,11,28]. Therefore, both genetically determined defects in the enzymes involved in the above reactions and a lack of vitamins B1, B6, B12 and folic acid in the diet can lead to pathological accumulation of homocysteine. In addition, an

increase in serum homocysteine can be observed with long-term use of drugs such as omeprazole , methylprednisolone, theophylline, metformin, cyclosporin A , isoniazid, sulfonamides, fibrates , nicotinic acid, H2 receptor antagonists, levodopa , carbamazepine , hydrogen pump blockers, aminofillin, estrogen-containing contraceptives , cytostatics, nitrous oxide and anticonvulsants. These drugs affect homocysteine metabolism pathways that require the participation of vitamins as cofactors or enzyme substrates. Some studies show that protein-rich food increases serum homocysteine levels by 10-15% after 6-8 hours, which explains the higher levels of homocysteine in the evening [6]. The accumulated knowledge on the metabolism of homocysteine was summarized by the international expert W. Herrmann in 2006 and published in the journal Clinical laboratory [17].

Despite the fact that prenatal HHC is the cause of deep functional disorders in the CNS of the offspring, as evidenced by the works published earlier by us [2], as well as by other domestic and foreign researchers [7], it is not completely clear what causes these disorders. and to what extent they are due to changes in the functional state of the placenta. It is important that HHC in the mother is accompanied, as noted in the above experimental studies, by an increase in the content of homocysteine in the blood of newborn animals. This indicates that homocysteine, which is formed in an increased concentration due to a violation of its metabolism, overcomes the fetoplacental and, possibly, the blood-brain barrier by simple diffusion or by binding to a specific receptor [8]. The authors of the studies carried out in this direction believe that the cause of the observed changes is the increased sensitivity of the cells of the nervous system to excitotoxic and oxidative damage induced by HHC, as judged on the basis of the obtained data on the suppression of the function of NMDA glutamate receptors [9], inhibition of the activity of antioxidant enzymes and a decrease in the content of low molecular weight antioxidants [1], a decrease in the survival of neurons with increased generation of reactive oxygen species [12], changes in the expression of neurotrophic factors BDNF and NGF [3], as well as proteins S-100B, GFAP and NCAM, which are markers of neuronal maturation and astrocytes . The above neurochemical disorders were found in the offspring of rats that underwent prenatal HHC on the 1st [3,4] and 10–12th days of postnatal development [7] and were combined with subsequent impairments of their cognitive functions on 45th [7] and 75th days of life [3]. The role of oxidative stress in HHC-induced disorders in the development of the nervous system and cognitive function of the offspring is also confirmed by the fact that they can be eliminated by administering melatonin and some short peptides with pronounced antioxidant properties to animals during pregnancy [2,3].

The most significant processes that reflect the functional state of the placenta, which are affected by HHC, include apoptosis. It has been established that homocysteine induces the processes of apoptosis and cell death in the trophoblast [15] and in the fetal brain [26], its proapoptotic effect is suppressed by the administration of folates [7].

According to the literature data, the mechanism of activation of apoptosis during HHC in various cell types can be carried out both “externally”, through the interaction of extracellular signals with cell surface receptors [18], and “internally”, associated with the destruction of mitochondria under the influence of oxidative stress, accompanied by the release of cytochrome C into the cytoplasm [19], which was noted, in particular, when homocysteine was exposed to trophoblast cells [24,28]. The mechanism of the proapoptotic action of homocysteine, according to most researchers, is due to the oxidative stress induced by it, since as a result of the action of homocysteine and its metabolic products, a significant amount of reactive oxygen species is formed that triggers the mechanism of cell death. It is interesting that neurotrophins expressed in the placenta, including BDNF [9], as well as melatonin, which inhibits both the external receptor and internal mitochondrial pathways of apoptosis in the trophoblast , have an antiapoptotic effect [20].

A few years ago, the World Health Organization recognized a homocysteine concentration of more than 10 μmol /l (relative norm) in adults as a borderline in the diagnosis of diseases, which made it possible to identify the desired disease in people at risk [3]. According to modern concepts, homocysteine is a nonproteinogenic amino acid with one methylene group [26,28]. Homocysteine is synthesized from methionine by removing the terminal methyl group. It is important to note that homocysteine does not come from food, is not a vitamin and is not part of the proteins of the human body. Normally, homocysteine is synthesized from methionine in a multi- step process. First, methionine is alkylated with adenosine triphosphate to form S- adenosylmethionine [3]. Then, using the enzyme cytinosyl-5-methyltransferase, S- adenosylmethionine transfers its methyl group to

cytosine to deoxyribonucleic acid, forming adenosylhomocysteine . The enzyme adenosylhomocysteinase then catalyzes the hydrolysis of this product to form homocysteine. Normally, due to the dynamic processes of remethylation and transsulfonation, the level of homocysteine remains stable.

Conclusion

Hyperhomocysteinemia is a common and modifiable risk factor for nephro- and cerebrovascular diseases. The literature data presented in the review confirm the contributing role of hyperhomocysteinemia in the development of pathology of the kidneys and cerebrovascular system, as well as the importance of taking into account, in this regard, disorders of homocysteine metabolism during primary and secondary prevention of athero- and thrombovascular complications. This involves maintaining a healthy lifestyle with the restriction of products that increase the level of homocysteine, adherence to the principles of a balanced diet with an increased intake of plant products rich in folic acid and B vitamins. It is also advisable to control the level of homocysteine in patients who take drugs that affect vitamin - folate status.

LIST OF REFERENCES:

1. Litvinenko I.V. Dementia and psychotic disorders inparkinsonism: common occurrence and new perspectives in therapy / I.V. Litvinenko // Advances in gerontology. - 2014. - Issue. 13. - S. 94-101.
2. Litvinenko I.V. Hyperhomocysteinemia in Par's diseaseKinson - a new variant of the complications of the therapy or a specific marker of the disease? / I.V. Litvinenko [et al.] // Annals of the wedge and experiment. Nevrol. - 2018. - V. 2, No. 2. - S. 13-17.
3. Lobzin V.Yu. Cerebral Metabolism A ssessment 18fluorodeoxyglucose in the early diagnosis of cognitive impairments / V.Yu. Lobzin [et al.] // Medline.ru. - 2013. - V. 14, No. 1. - S. 1057-1070.
4. Polushin A.Yu. Hyperhomocysteinemia is a predictor of severitystroke against the background of extensive damage to the medulla / A.Yu. Polushin [and others] // Vestn. Ross. military-med. acad. - 2013. - No. 4 (44). - S. 89-94.
5. Allen L.H. Causes of vitamin B12 and folate deficiency / LH Allen // Food Nutr . Bull. - 2018. - Vol. 29. - S. 20-34.
6. Hooshmand B. Homocysteine and holo-transcobalamin and therisk of Alzheimer disease: a longitudinal study / B. Hooshmand [et al.] // Neurology. - 2010. - Vol. 75. - P. 1408-1414.
7. Morris M.S. Folate and vitamin B-12 status in relation to anemia, macrocytosis and cognitive impairment in older Americans in the age of folic acid fortification / MS Morris [et al.] // Am. J.Clin. Nutr. - 2017. - Vol. 85. - P. 193-200.
8. Nilsson K. Plasma homocysteine is elevated in elderly patientswith memory complaints and vascular disease / K. Nilsson, L. Gustafson, B. Hultberg // Dement. Geriatr Cogn Discord . - 2007. - Vol . 23. - P. 321-326.
9. Nurk E. Plasma total homocysteine and memory in the elderly:the Hordaland homocysteine study / E. Nurk [et al.] // Ann. Neurol . - 2005. - Vol . 58.-P 847-857.
10. Prins ND Homocysteine and cognitive function in the elderly:the Rotterdam Scan Study / ND Prins [et al.] // Neurology. - 2002. - Vol. 59. - P. 1375-1380.
11. Dhobale MV, Pisal HR, MehendaleJoshi SR Differential expression of human placental neurotrophic factors in preterm and term deliveries. // Int. J. Dev. Neurosci. 2013; 31(8): 719-23. https://doi . org /10.1016/j.ijdevneu.2013.09.006
12. Garces MF, Sanchez E., Torres-Sierra AL, Ruiz-Parra AI, Angel-Muller E., Alzate JP, Sanchez AY, Gomez MA, RomeroC., Castaneda ZE, Sanchez- Rebordelo E., Dieguez C., Nogueiras R., Caminos JE Brain-derived neurotrophic factor is expressed in rat and human placenta and its serum levels are similarly regulated throughout pregnancy in both species. // Clinic Endocrinol .(Oxf .). 2014; 81(1): 141-51. https://doi.org/10.1111/cen.12391
13. Tometten M., Blois S., Arck PC. Nerve growth factor in reproductive biology: link between the immune, endocrine and nervous system? // Chem Immunol Allergy 2005; 89:135-48. https://doi . org /10.1159/000087962

14. Mayeur S., Lukaszewski MA, Breton C., Storme L., Vieau D., Lesage J. Do neurotrophins regulate the feto -placental development? // Med Hypotheses 2011; 76(5): 726-8. https://doi.org/10.1016/j . mehy2011.02.008
15. Dhobale M. Neurotrophins: Role in adverse pregnancy outcome. // Int. J. Dev Neurosci . 2014; 37:8-14. https://doi.org/10.1016/j . ijdevneu.2014.06.005
16. Meeker R., Williams K. Dynamic nature of the p75 neurotrophin receptor in response to injury and disease. // J. Neuroimmune Pharmacol 2014; 9(5): 615-28. https://doi. org /10.1007/s11481-014-9566-9
17. Teng KK, Felice S., Kim T, Hempstead BL Understanding proneurotrophin actions: Recent advances and challenges. // Dev Neurobiol 2010; 70(5): 350-9. https://doi. org /10.1002/dneu.20768
18. Fujita K., Tatsumi K., Kondoh E., Chigusa Y., Mogami H., Fujii T., Yura S., Kakui K., Konishi I. Differential expression and the anti- apop - totic effect of human placental neurotro - phins and their receptors. // Placenta 2011; 32(10): 737-44. https://doi.org/10.1016/j. placenta.2011.07.001
19. Kawamura K., Kawamura N., KumazawaY. , Kumagai J., Fujimoto T, Tanaka T Brain-derived neurotrophic factor/tyrosine kinase B signaling regulates human trophoblast growth in an in vivo animal model of ectopic pregnancy. // Endocrinology .2011; 152(3): 1090-100. https://doi.org/ 10.1210/en. 2010-1124
20. Kawamura K., Kawamura N., Sato W., Fuku da J., Kumagai J., Tanaka T. Brain-derived neurotrophic factor promotes implantation and subsequent placental development by stimulating trophoblast cell growth and survival. // Endocrinology 2009; 150(8): 3774-82. https://doi.org/10.1210/en.2009-0213
21. Mayeur S., Silhol M., Moitrot E., BarbauxBreton C., Gabory A., Vaiman D., Dutriez-Casteloot I., Fajardy I., Vamber - gue A., Tapia- Arancibia L., Bastide B., Storme L., Junien C., Vieau D., Lesage J. Placental BDNF/ TrkB signaling system is modulated by fetal growth disturbances in rat and human. // Placenta 2010; 31(9): 785-91. https://doi.org/10.1016/j.placenta.2010.06.008
22. Sahay AS, Sundrani DP, Wagh GN, Mehendale SS, Joshi SR Neurotrophin levels in different regions of the placenta and their association with birth outcome and blood pressure. // Placenta 2015; 36(8): 938-43. https://doi.org/10.1016/j . placenta.2015.06.006
23. Toti P, Ciarmela P, Florio P, Volpi N., Oc - chini R., Petraglia F Human placenta and fetal membranes express nerve growth factor mRNA and protein. // J. Endocrinol Invest. 2006; 29(4):337-41. https://doi . org /10.1007/BF03344105
24. Sahay AS, Sundrani DP, Joshi SR Neurotrophins: role in placental growth and de velopment. // Vitam Horm. 2017; 104:243-61.
25. Lazarovici P, Marcinkiewicz C., Lelkes P.I. Cross talk between the cardiovascu lar and nervous systems: neurotrophic effects of vascular endothelial growth factor (VEGF) and angiogenic effects of nerve growth factor (NGF)-implications in drug development. Curr Pharm Des. 2006; 12(21):2609-22. https://doi. org /10.2174/138161206777698738
26. Oosterbaan AM, Steegers EA, Ursem NT The effects of homocysteine and folic acid on angiogenesis and VEGF expression during chicken vascular development. // Mi - crovasc. Res. 2012; 83(2):98-104. https://doi.org/10.1016/j.mvr.2011.11.001
27. Xu X., Yang XY, He BW, Yang WJ, Cheng WW Placental NRP1 and VEGF expres sion in pre-eclamptic women and in a homocysteine-treated mouse model of pre-eclampsia. // Eur. J. Obstet. Gynecol. reproduction. Biol. 2016; 196:69-75. https://doi. org/10.1016/j.ejogrb.2015.11.017
28. Dammann O., Bueter W, Leviton A., Gressens P, Dammann CE Neuregulin-1: a potential endogenous protector in perinatal brain white matter damage. // Neonatology. 2008; 93(3):182-7. https://doi.org/10.1159/000111119

Entered 20.04.2023