neurofibromatosis 1: a retrospective register-based total population study / J. Leppävirta, R.A. Kallionpää, E. Uusitalo [et al.] //Orphanet J Rare Dis. 2018 Jan 15; 13(1):5.
15. Delvecchio K. Surgical resection of rare internal jugular vein aneurysm in neurofibromatosis type 1 / K. Delvecchio, F. Moghul, B. Patel, S. Seman //World J Clin Cases. 2017 Dec 16; 5(12):419-422. doi: 10.12998/wjcc.v5.i12.419.
16. Fdil S. Spontaneous hemothorax: a rare complication of neurofibromatosis type 1/ S. Fdil, S. Bouchikhi, J.E. Bourkadi /Pan Afr Med J. 2017 Sep 27; 28:85. 10.11604/pamj.2017.28.85.13820. eCollection 2017. French.
17. Friedman J.M. Neurofibromatosis 1 // GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. 1998 Oct 2 [updated 2018 Jan 11].

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GENETIC AND EXTERNAL ENVIRONMENTAL RISK FACTORS FOR CONGENITAL HEART DISEASE IN CHILDREN (LITERATURE REVIEW)

ABSTRACT

The article presents a literature review of main risk factors of the development of congenital heart defects in children - genetic and environmental ones.

Keywords: congenital heart disease, children, risk factors, genetics, environment, pollutants.

Genetic risk factors for congenital heart disease in children. Genetically determined mechanisms of formation of congenital anomalies in the fetus include violations of maturation of male and female gametes, as well as pathology of intrauterine development. A variety of mutations (chromosome rearrangements such as translocations, inversions) damage the conjugation of chromosomes in meiosis and the death of maturing germ cells in the meiosis stage. Persons with chromosomal diseases (Down's disease, Klinefelter's syndrome) have severe spermatogenesis disorders associated with the defeat of the AZF locus gene complex located in the long arm of the male Y chromosome, mutations in the CFTR gene or the androgen receptor (AR) gene [6, 3].

The ovum of the female organism is even more sensitive to various exogenous and endogenous factors for several decades, which is associated with the complexity and long duration of hormonal regulation of the processes of oogenesis [1, 21]. Therefore, the prevention of hereditary conditioned congenital pathology should, first of all, be aimed at preserving women's health.

The formation of congenital developmental anomalies can be caused by the influence of damaging factors of different nature during preembryonic development (20 days from the moment of conception), embryonic (up to the 12th week of pregnancy) and fetal development [23]. Critical periods at this stage are implantation and placentation, when the selection of damaged embryos takes place [1].

Anomalies of fetal development, according to some studies, are associated with polymorphism of folate metabolism genes, since mutant genes can cause hyperhomocysteinemia, which has an embryotoxic effect. In addition, the deficiency of methyl groups is thus capable of altering the processes of cell proliferation and differentiation, making it more difficult to divide chromosomes during oogenesis [25]. The study of the polymorphism of folate cycle genes (*MTHFR, MTRR* genes) in families in which births of children with congenital heart diseases were observed showed a significant increase in the frequency of carriage of the MTHFR 677T allele in women and the MTRR 66G allele in men. The authors explain the negative effect of these alleles on embryogenesis by pathological changes in fetal cell division and differentiation during methylation failure [12].

Similar results were obtained in another study of the relationship of MTHFR 677T polymorphism and the risk of developing congenital malformation. The relative risk in fetal analysis was 1.26 without clear evidence of heterogeneity and 1.52 in the analysis of mothers with significant heterogeneity of the results [18].

In the genesis of congenital heart disease, the state of connective tissue in the process of ontogenesis is of great importance, since it is precisely involved in the construction of the heart's framework. The effects of various damaging factors, as well as genetic conditioning, can lead to connective tissue dysplasia and cardiac dysplasia. Atypically located chords of the left ventricle, prolapse of the mitral and tricuspid valves, aneurysm of the

interatrial septum prevail in the structure of congenital heart defects associated with connective tissue dysplasia [11]. Hereditary genesis of congenital developmental anomalies is confirmed by the fact that the risk of developing congenital heart disease significantly increases with twin monochorionic pregnancies [20] and closely related marriages [27].

Genetic and epidemiological studies in recent decades have contributed to the elucidation of the relationship between the prevalence of many diseases and the ethnicity of the population. In the study of hereditary diseases, it was found that differences in incidence rates, clinical picture and disease outcomes are associated with the frequency of alleles of genes responsible for the development of the disease in ethnic groups [24]. It was found that mutations of alleles, detected with a frequency of less than 2%, are, as a rule, specific for individual ethnic groups. For the population of ethnic groups of the Russian Federation, there are also significant differences in adaptation reactions, physiological and morphological indicators [4, 13]. In modern conditions, due to interethnic marriages, the introduction of the European component into the gene pool of ethnic groups of northern peoples is observed, which can change the functioning of physiological systems and predispositions to different classes of diseases [17, 9].

External environmental risk factors for congenital heart disease in children. The development of economic activities throughout the world has now led to large-scale environmental pollution of production waste. Toxic substances through the ecological chain enter the human body, having various adverse effects, including teratogenic. The most vulnerable to their impact are the body of pregnant women and children. The issue of the effect of environmental toxic substances and other anthropogenic risk factors on the cardiovascular system of the embryo and fetus is still not fully understood, which is associated with difficulties in establishing threshold exposure and dose dependence of the formation of congenital malformation [22]. The most pronounced teratogenic effect in relation to the cardiovascular system is established for ionizing radiation. At the heart of hereditary disorders in individuals exposed to radiation exposure are chromosomal, genomic and dominant gene mutations in both somatic and sexual cells. Mutational changes in somatic cells cause destabilization of the genome, a decrease in functional and reparative capabilities of DNA, and immunological resistance of the organism. Developmental malformations are caused by genetic changes in the sex cells. Thus, studies conducted on samples including descendants of the first generation of the liquidators of the Chernobyl accident showed a high prevalence among them of congenital anomalies and malformations - 2.5 times higher than in the Russian population as a whole. Among the population living in radiation-contaminated territories, this indicator exceeded the all-Russian level by 2.8 times. 46.1% of the children of the liquidators of the accident with the detected chromosomal aberrations had abnormalities of development, including congenital heart disease [8]. Industrial emissions to atmospheric air due to the operation of industrial enterprises in the chemical and petrochemical industries are also reflected in an increase in the prevalence of congenital heart disease among the population living in contaminated areas. Thus, in a study conducted in industrial regions of the Republic of Tatarstan, a direct correlation was established between the increase in the incidence of congenital heart diseases and the total release of industrial toxic substances described by the regression equation: congenital heart disease = 0.469 + 0.003 x NE [14]. The effect of toxic industrial emissions in the pathogenesis of the development of congenital malformations can be explained by mutagenesis of the sex cells of parents or somatic cells of their descendants, the disturbance of mitotic processes, damage to energy processes and cell membranes in the fetus, which eventually leads to cardiac dysfunction at various stages of organ formation [10].

In the Republic of Sakha (Yakutia) in recent years, the growth of anthropogenic pollution of atmospheric air by solid, liquid and gaseous products of industrial production, in the structure of which solids, carbon monoxide, nitric oxide, sulfur dioxide and hydrocarbons prevail. In the industrially developed regions of the republic, a statistically significant increase in morbidity rates of congenital anomalies, deformations and chromosomal abnormalities, including CHD, was established [2]. These data are consistent with the results of a study in the city of Belgorod. The highest prevalence of CHD was observed in areas with a high content of pollutants, such as nitrogen dioxide, inorganic dust, carbon monoxide, which are unfavorable for the ecological state of the air basin, with a load of 12.0 tons per year per newborn [5].

In the regions of developed agricultural production of the Stavropol Territory of the Russian Federation, land contamination with copper, cadmium, nickel, pesticides, as well as a high content of nitrites and nitrates in drinking water. At the same time, the results of medical and hygienic monitoring indicate a steady increase in the prevalence of congenital malformations in newborns and children, one third of whom are in the CHD [7].

Chinese researchers established a direct relationship between the exposure of pregnant women to ozone and carbon dioxide in the first trimester of pregnancy and the development of interventricular septal defects and tetralogy of Fallot in newborns [26].

Data from twelve epidemiological studies suggest that the risk of developing CHD in newborns increases five to six times when exposed to an industrial solvent of trichlorethylene on the mother's body during pregnancy [19]. The risk of congenital heart diseases increased also with the professional effect of nickel on the body of the fathers (RR = 1.28) [15].

Studies of the etiological association of anthropogenic and occupational factors on the parents' organism and the development of congenital circulatory anomalies in their offspring are important not only for studying the pathogenetic features of teratogenesis, but also for the development and implementation of preventive programs in ecologically unfavorable territories.

Thus, on the basis of literature data, one can conclude that genetic and external environmental factors are one of the main risk factors for the CHD development; are of great importance in assessing and predicting the causes that have a negative impact on the reproductive health of the population and increase the risk of development congenital heart defects in children.

REFERENCES:

1. Ajlamazyan EH.K. Baranov V.S. Prenatal'naya diagnostika nasledstvennyh i vrozhden¬nyh boleznej [Prenatal diagnosis of hereditary and congenital diseases]. Moscow: MEDpress-inform [M.: Medpress-inform]. 2005, 415 p.
2. Astaf'ev V.A. Ushkareva O.A. Semenova N.P. Zagryaznenie atmosfernogo vozduha i zabolevaemost' naseleniya respubliki Saha (Yakutiya) [Pollution of atmospheric air and morbidity of the population of the Republic of Sakha (Yakutia)] Byulleten' VSNC SO RAMN [the Bulletin of East Siberian scientific center SB RAMS]. 2013,

V. 94, №6, P. 92-96.
3. Baranov A.A. Al'bickij V.YU. Il'in A.G. O rezervah snizheniya smertnosti detskogo naseleniya [On the reserves to reduce the mortality of children] Voprosy sovremennoj pediatrii [Issues of modern pediatrics]. 2006, V. 5, №. 5, P. 5-7.
4. Boyko E.R. Fiziologo-biohimicheskie osnovy zhiznedeyatel'nosti cheloveka na Severe [Physiological and biochemical foundations of human life in the North]. Ekaterinburg: UrB RAS, 2005, 210p.
5. Verzilina I.N. Agarkov N.M. Churnosov M.I. Rasprostranennost' i struktura vrozhdennyh anomalij razvitiya u novorozhdennyh detej g. Belgoroda [Prevalence and structure of congenital developmental anomalies in newborn children in Belgorod] Pediatriya [Pediatrics]. 2009, V. 87, № 2, P. 151-154.
6. Ginter E. K. Medicinskaya genetika [Medical genetics]. Moscow: Medicine, 2003, 448p.
7. Dement'eva D.M., Bezrodnova S.M. Problema vrozhdennyh porokov razvitiya u detej v regione s neodnoznachnoj ehkologicheskoj situaciej [The problem of congenital malformations in children in a region with an ambiguous environmental situation] Gigiena i sanitariya [Hygiene and Sanitation] . 2013, № 1.- P. 61-64.
8. Ibragimova A.I. Klinicheskie dannye o genotoksicheskom dejstvii ioniziruyushchej radiacii [Clinical data on the genotoxic effect of ionizing radiation] Ros. vestn. perinat. i pediatrii [Ros. known. perinatum. and pediatrics]. 2003, № 6, P. 51-55.
9. Krivova N.A., Chanchaeva E.A. Antioksidantnaya aktivnost' plazmy krovi u aborigenov nizkogor'ya i srednegor'ya Yuzhnogo Altaya [Antioxidant activity of blood plasma in aboriginal lowlands and mid-mountains of the Southern Altai] Fiziologiya cheloveka [Physiology of man]. 2011, № 2, P. 60-65.
10. Kucenko S. A. Osnovy toksikologii [Foundations of Toxicology] SPb.: OOO Izd-vo «Foliant» [SPb .: Open Company Publishing house "Foliant"]. 2004, 720p.
11. Men'shikova L.I. Surova O.V., Makarova V.I. Displaziya soedinitel'noj tkani serdca v geneze kardiovaskulyarnoj patologii u detej [Dysplasia of the connective tissue of the heart in the genesis of cardiovascular pathology in children] Vestnik aritmologii [Bulletin of arrhythmology]. 2000, №19, P. 54-56.
12. Fetisova I.N. Peretyatko L.P., Dyuzhev ZH.A. [i dr.] Polimorfizm genov folatnogo cikla v sem'yah s privychnym nevynashivaniem beremennosti, porokami razvitiya ploda i anehmbrioniej [Polymorphism of folate cycle genes in families with habitual miscarriages, fetal malformations and anembryonia] Vestnik RUDN, seriya Medicina [Bulletin of RUDN, series Medicine]. 2009, № 6, P. 11-18.
13. Kolesnikova L.I. Darenskaya M.A., Dolgih V.V. [i dr.] Pro- i antioksidantnyj status u podrostkov-tofov i evropeoidov [Pro- and antioxidant status in sub-growths-tophics and Caucasoids] Izvestiya Samarskogo NTS RAS [Proceedings of the Samara Scientific Center of the Russian Academy of Sciences]. 2010, T. 12, № 1-7, P. 1687-1691.
14. Nasyrova K.I. Mirolyubov L.M., Kalinicheva YU.B. [i dr.] Regional'naya zabolevaemost' vrozhdennymi porokami serdca v svyazi s zagryazneniem atmosfernogo vozduha promyshlennymi vybrosami [Regional morbidity of congenital heart defects due to industrial air pollution of atmospheric air] Prakticheskaya medicina [Practical medicine]. 2008, T.28 , №4, P. 72-74.
15. Nikanov A.N. Talykova L.V., Rocheva I.I. [i dr.] Rol' proizvodstvennyh faktorov riska v formirovanii reproduktivnyh ehffektov u rabotnikov nikelevyh predpriyatij krajnego severa [The role of production risk factors in the formation of reproductive effects among employees of nickel enterprises in the Far North] EHkologiya cheloveka [Ecology of the person]. 2009, №6, P. 44-46.
16. Sipyagina A.E. Osobennosti formirovaniya vrozhdennyh porokov razvitiya u detej iz semej likvidatorov radiacionnoj avarii [Features of formation of congenital malformations in children from families of liquidators of a radiation accident]. Ros. vestn. perinat. i pediatrii [Ros. known. perinatum. and pediatrics.]. 2005, №2, P. 53-56.
17. Fefelova V.V. Voprosy proiskhozhdeniya mongoloidov Sibiri i vliyanie otdalennyh posledstvij autbridinga na predraspolozhennost' ehtih populyacij k zabolevaniyam [Questions of the origin of Mongoloidal Siberia and the influence of remote consequences of outbreeding on the predisposition of these populations to diseases] The Bulletin of the Siberian Branch of the Russian Academy of the Medical Sciences: Thesis of the 13th international congress on circumpolar health. Novosibirsk, 2006, P. 88-89.
18. Li.Z, Jun Y., Zhong-Bao R. [et all] Association between MTHFR C677T polymorphism and congenital heart disease. A family-based meta-analysis. Herz. -2015,Vol. 40, Suppl. 2, P. 160-167.
19. 19. Bukowski J. Critical review of the epidemiologic literature on the association between congenital heart defects and exposure to trichloroethylene. Rev Rev Toxicol., 2014, Vol. 44, № 7, P.581-589.
20. Campbell K., Copel J., Ozan Bahtiyar M. Congenital heart defects in twin gestations, Minerva Ginecol., Vol. 61, № 3, P.239-244.
21. Golubovsky M. D. Manton K. Oocytes physically and genetically link three generations: genetic demographic implications. Environment and perinatal medicine, SPb., 2003, P. 354-356.
22. Foster W.G., Evans J.A., Little J. [et all] Human exposure to environmental contaminants and congenital anomalies: a critical review. Crit Rev Toxicol. 2016, №11, P.1-26.
23. Fung A., Manlhiot C., Naik S. [et all] Impact of prenatal risk factors on congenital heart disease in the current era. J Am Heart Assoc. 2013, Vol. 31, № 2: e000064.
24. 24. Kaufman J.S. Cooper R.S. Considerations for the use of racial / ethnic classification in the etiologic research. Am. J. Epidemiol. 2001, Vol. 154, P. 291-298.
25. Martinelli M. Scapoli L., Pezzetti F. C677T variant form at the MTHFR gene and CL . P: a risk factor for mothers?. Am. J. Med. Genet. , 2001.,Vol. 98, P. 357-360.
26. Zhang B. Zhao J., Yang R. [et all] Ozone and Other Air Pollutants and the Risk of Congenital Heart Defects . Sci Rep., 2016, № 6. P. 348-352.
27. Shieh J.T. Bittles A.H., Hudgins L. Consanguinity and the risk of congenital heart disease . Am J Med Genet A, 2012, Vol.158A (5), P.1236-1241.

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