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ASSESSMENT OF THE CONTRIBUTION OF ENVIRONMENTAL FACTORS AND INTERLEUKIN-10 GENE POLYMORPHISMS TO THE FORMATION OF ITS SERUM LEVELS

ABSTRACT

Air pollution has an impact on the health of the population and leads to an increased risk of developing pathology, including the immune system. Genetic predisposition also contributes to the development of disorders in this system. The purpose was to study the contribution of the chemical inhalation load and gene polymorphisms of IL-10 in the formation of his serum levels in adolescents. Polymorphisms -1082G/A, -592C/A, -819C/T of gene IL-10 and the content of its protein product in the blood were studied in schoolchildren who live under conditions of varying levels of air pollution. It has been established that air pollution by immunotropic compounds plays the dominant role in the formation of the serum level of IL-10 in healthy adolescents. The effect of the polymorphic loci of the IL-10 gene (-592C/A and -819C/T) on the formation of its level is manifested in conditions of a high inhalation chemical load.

Keywords: gene polymorphism, interleukin-10, adolescents, air pollution.

Introduction. At the last time the data on the effect of air pollution on public health, the development of the pathology of the immune system is convincing. The impact of environmental factors of the same intensity and duration in some cases leads to the development of pathological processes, in other cases they do not lead to pathology. This is due to a combination of factors, among which the most important are the state of the body during impact and genetic predisposition or resistance to the development of certain diseases. The impact on the body of adverse environmental factors in critical periods of its development, which include the formation and restructuring of systems in childhood and adolescence, can cause the development of an inadequate response and cause the formation of pathology in the future.

The immune system plays an important role in the development of compensatory and adaptive reactions in response to the impact of external factors. In the development of the immune response, the production of inflammatory and anti-inflammatory cytokines (interleukins and interferons) is activated [10]. Changes in the level of cytokine synthesis, which is genetically determined, can lead to a decrease in anti-infective protection, the development of an excessive inflammatory or allergic process and cause the occurrence of pathology [2, 9, 13].

Based on the above-stated facts, this work purposed to study the contribution of the interleukin-10 gene polymorphism and chemical inhalation load to the formation of IL-10 serum levels in adolescents.

Materials and methods. The medical examination of adolescents was conducted after parents (legal representatives) gave their written informed consent in accordance with the requirements of the Committee on Biomedical Ethics. The work consisted in conducting a one-stage survey of 650 schoolchildren of 14.76 ± 0.06 years who live in the territory of Eastern Siberia under the same climatic and geographical conditions, but with different levels of air pollution. Adolescents had no exacerbation of chronic diseases and acute respiratory infections at the time of the survey. Teenagers were divided into groups according to hazard index (HI) immunity disorders. When calculating the hazard index, a formula was used to estimate the dose chemical inhalation load [7]. We introduced personified data on each teenagers, data on admixture concentrations in the atmospheric air, and indoor concentrations of priority pollutants (both at home and in an educational organization) into a formula for calculating a dose chemical inhalation burden [4]. The first group was made up of 225 school students with HI lower than 2; the second group was made up of 359 teenagers with HI equal to 2 or higher, but less than 3, the third group include 66 adolescents with HI equal to 3 or higher.

We examined concentrations of interleukine-10 (IL-10) in blood serum. Cytokine levels were determined via ELISA tests with test-systems (Vector-Best", Novosibirsk). The allelic variants –1082G/A, –592C/A, and –819C/T of gene IL-10 were examined by PCR in real time in accordance with the protocol of the manufacturer of reagent kits (NPF Litekh, Russia). DNA for genetic studies was isolated from whole blood leukocytes with reagent «DNA-express» (NPF Litekh, Russia) using a modified method [1].

We analyzed the results statistically with "Statistica 6.0" applied software. A check on the normal distribution of quantitative indicators was made using the Shapiro-Wilk test. The content of IL-10 in the blood of adolescents of groups I, II and III was compared by non-parametric tests of Kruskel-Wallis and the U-test of Mann-Whitey. We identified the dependence of the level of IL-10 on the inhalation chemical load and the polymorphisms of its gene were performed using nonlinear regression. The distribution of the genotypes was tested for compliance with the Hardy-Weinberg equilibrium in the program www. oege.org/software/hwe-mr-calc.shtml. the Hardy–Weinberg equilibrium calculator. The presence of differences in the distribution of the frequencies of the genotypes in the surveyed groups was evaluated according to the chi-squared test ($\chi 2$). A p value equal to 0.05 was considered to be a critical statistical significance of discrepancies for Kruskel-Wallis tests, $\chi 2$ test and regression analysis. For the Mann-Whitney U test, the level of statistical significance of the differences, taking into account the Bonferroni amendment, was 0.017. The research results are given as a median and 25 – 75 quartiles (Me(LQ-UQ)).

Results and discussion. It was found that the mean group values in blood IL-10 adolescents were within reference levels (0-10 pg / ml). These results confirm that the examined adolescents were practically healthy and did not have inflammatory processes. We found differences in its concentration depending on the level of inhalation load of immunotropic substances.The content of IL-10 in group II was statistically significantly higher than in group I (2.51 (0.24 - 5.95) pg / ml, p = 0.014) and was 3.33 (1.36 - 6.44) PG / ml. The level of this parameter in group III was lower than in group II (1.39 (0.01 -

4.22) pg / ml, p = 0.002). Changes in the concentration of IL10 may result from the activation of immunity at 2≤HI <3 and its stress at a higher level of air pollution by chemical compounds [6, 8, 12].

It is known that nucleotide substitutions at polymorphic loci -592 C/A and -819 C / T and -1082G / A of the *IL-10* gene are associated with low production of its protein. In this regard, the carriage of the minor alleles of these polymorphisms may cause a reduced concentration of IL-10, cause an imbalance between inflammatory and anti-inflammatory processes, change the course of the inflammatory response to external influences. [3, 5, 11]. We evaluated the frequency of genotypes of -592 C/A and -819 C/T and -1082G/A polymorphisms of the *IL-10* gene. The distribution of genotypes among schoolchildren in each group was in compliance with the Hardy–Weinberg equilibrium. There were no statistically significant differences in the levels of IL-10 in the blood of adolescents depending on the polymorphic variants of the gene (Table 1). This is understandable, since the observed schoolchildren were healthy and they did not have an activation of the synthesis of inflammatory and anti-inflammatory cytokines, in which there could be a decrease in protein synthesis due to the presence of minor alleles. It is possible that under conditions of increased chemical inhalation load with immunotropic compounds, which was accompanied by changes in the levels of IL-10 in the blood of adolescents, the contribution of genetic factors to the formation of its content will be more significant. Analysis of the content of IL-10 in schoolchildren with different HI immunity disorders depending on genotypes was carried out on the basis of this assumption (Table 1).

Differences in serum levels of IL-10 in adolescents of the first, second and third groups, depending on the presence of the major and minor alleles of the polymorphisms -1082G/A, -592C/A and -819C/T of the *IL-10* gene, were not detected. However, the content of this indicator in the blood of adolescents of group I differed from that in groups of teenagers who had the same genotypes, but were exposed to higher levels of air pollution. The concentration of IL-10 in the blood of adolescents with the GG and GA genotypes of the for polymorphic loci -1082G/A of gene *IL-10* of group II was higher than that of schoolchildren with the same genotypes from group I (p = 0.0004 and p = 0.0101, respectively). A similar situation was observed for the polymorphism -592C/A.

Among individuals with CC genotype, the highest level of IL-10 was observed in group II (p = 0.0002 and p = 0.023 compared with groups I and III, respectively). Differences in the content of the protein product between groups were not observed if the adolescents had a minor allele A (genotypes CA and AA). The analysis the concentration of IL-10 in schoolchildren with different polymorphic variants in the -819 position revealed higher levels of this indicator were also found in individuals with genotypes CC and CT of group II compared with their peers from group I (p = 0.006 and p = 0.033, respectively) and III (p = 0.030 and p = 0.053, respectively).

Thus, it was found that the level of IL-10 among schoolchildren of Group I was lower than that of their peers, who have a greater inhalation chemical load. These differences were most pronounced in homozygous carriers of the "wild" allele (genotypes GG and GA polymorphism -1082G/A, genotypes CC and CA polymorphic locus -592C/A and genotypes CC and CT polymorphism -819C/T of the *IL-10* gene). Consequently, the polymorphisms -1082G/A, -592C/A and -819C/T of the *IL-10* gene make a significant contribution to the formation of the level of its protein product in adolescents with an increased level of inhalation chemical load (HI≥2).

A regression analysis was performed to assess the contribution of genetic factors to the formation of IL-10 levels. It is important that adequate models describing the contribution of the -1082G/A polymorphism of the *IL-10* gene to the formation of IL-10 level in blood were not detected. We studied the combined effect of air pollution by chemical compounds and the presence of single nucleotide substitutions in the -592C/A and -819C/T loci of the *IL-10* gene on the blood cytokine content. It was found that at HI<3, the values of β-coefficients were higher for variables that reflect the level of chemical inhalation load, compared with coefficients at indicators characterizing the contribution of the polymorphism -592C/A of the *IL-10* gene. This may indicate the dominant role of air pollution under the conditions of chemical inhalation load, which is no more than 3 times the reference levels (HI<3). The regression equation for group I was as follows $IL\text{-}10 = 0{,}20 + 0{,}228*(HI)^2 - 0{,}10*(P_{592})^2$ (R^2=0,06, p<0,005, F(2,18)=5,14). Regression equations for group II and III are $IL\text{-}10 = 38{,}81 - 0{,}14*HI - 0{,}11*P_{592}$ (R^2=0,03, p<0,051, F(2,17)=2,83) and $IL\text{-}10 = -4{,}13 + 3{,}50*\Pi_{592} - 0{,}58*\Pi_{819} - 0{,}41*(HI)^2 - 2{,}82*(\Pi_{592})^2$ (R^2=0,46,

IL-10 concentrations in teenagers depending on genotype, pg/ml

Polymorphism	Genotype	Overall samplingn =650	including			p_1
			Group I n=225	Group II n=359	Group III n=66	
-1082G/A	GG	3.25 (1.31-7.71)	2.51 (0.14-6.19)	5.08 (2.76-6.97)*I	4.07 (1.39-4.86)	0.002
	GA	3.36 (0.89-6.45)	2.75 (0.14-5.95)	3.56 (2.20-6.95)*I	3.82 (0.27-8.82)	0.040
	AA	3.69 (1.17-6.71)	2.70 (0.27-5.49)	4.07 (3.05-9.54)	5.32 (1.02-9.61)	0.171
p_2		0.464	0.922	0.488	0.958	
-592C/A	CC	3.85 (1.62-7.30)	2.70 (0.25-5.95)	4.33 (2.70-7.50)*I	2.11 (1.02-4.86)#II	0.000
	CA	3.56 (0.95-6.57)	3.09 (0.27-6.44)	3.88 (2.54-6.45)	4.22 (0.00-13.03)	0.165
	AA	3.39 (1.06-6.45)	2.07 (0.27-3.32)	6.60 (3.22-7.30)	4.07 (4.07-4.07)	0.150
p_2		0.766	0.851	0.489	0.647	
-819C/T	CC	2.78 (1.08-5.08)	2.70 (0.19-6.30)	3.56 (2.03-6.96)*I	2.11 (0.27-4.86)#II	0.009
	CT	3.26 (0.81-6.45)	2.50 (0.22-5.76)#II	3.54 (1.44-6.50)	1.02 (0.00-4.22)	0.030
	TT	3.32 (0.85-6.45)	1.35 (0.35-2.78)	4.77 (1.99-5.67)	3.57 (3.57-3.57)	0.116
p_2		0.879	0.733	0.602	0.751	

Note: p1 – the level of statistical significance of differences between groups I-III; p2 – the level of statistical significance of differences between subgroups of individuals with different genotypes; *I – the differences are statistically significant compared with the group I. p<0.017; #II – trend towards differences compared with group II. 0.017<p<0.033.

p<0,016, F(4,19)=4,20) respectively. In these equations, R^2 is the coefficient of determination, F- Fisher's criterion, P_{592} and P_{819} are variables that characterize the polymorphic variants -592C/A and -819C/T of the *IL-10* gene. The values 1, 2, and 3 were used to encode them. The number 1 was used to encode homozygotes for allele 1, number 2 for heterozygotes, and 3 for homozygotes for allele 2. The influence of genetic factors on the level of IL-10 increased when HI≥3, and was more dependent on the presence of nucleotide substitutions in the polymorphic loci -592C/A and -819C/T. The equations that were presented confirm this.

The values of the coefficients of determination of equations for groups I and II were analyzed. The contribution of chemical air pollution by immunotropic compounds and nucleotide substitutions in polymorphic loci of the IL-10 gene is 3-6% in the variability of IL-10 levels in practically healthy adolescents with personalized HI immunity disorders less than 3. With HI≥3, the role of chemical and genetic factors increases, and their combined effect causes changes in the serum IL-10 content in 41% of the schoolchildren examined.

Obviously, the presented regression models have a number of uncertainties associated with errors of analysis, a limited range of predictors, and the possibility of the modifying effect of unaccounted factors. Also, models have limitations. They can predict the contribution of these chemical and genetic factors to the variability of IL-10 levels with a probability of 95%, provided that adolescents have no acute infectious and inflammatory processes and personalized HI immunity disorders are less than 4. Also a necessary condition for the application of these regression equations is the similarity of the quantitative and qualitative composition of air pollutants with immunotropic effect, with that for which the model was made. These models allow us to prove the relationship between changes in the content of IL-10 in the serum of practically healthy adolescents and exposure to environmental factors, the polymorphism of the *IL-10* gene. Also, these models allow to establish the contribution of these factors to the formation of the level of IL-10, despite the limitations and uncertainties.

Conclusion. In general, the work found that the level of IL-10 changes in healthy adolescents when living in conditions of elevated levels of chemical inhalation immunotropic compounds. Differences in its content are most pronounced in homozygous carriers of the "wild" allele (allele G is for polymorphism -1082G/A, allele C is for polymorphic loci -592C/A and -819C/T of the *IL-10* gene). Using regression models, it was found that the contribution of air pollution and the presence of minor alleles of the polymorphisms -592C / A and -819C / T of the IL-10 gene contribute to the formation of IL-10 levels from 3 to 6% under the condition HI <3. When HI≥3, the role of these polymorphisms increases, the contribution of the combined influence of chemical and genetic factors in the variability of IL-10 content reaches 41%.

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MORPHOMETRIC CHARACTERISTICS OF CEREBRAL CORTEX GYRUS PRECENTRALIS IN THE MALES-MESOCEPHALIC ACCORDING TO CT - SCAN

ABSTRACT

The **purpose** of research was to determine the width of the precentral gyrus, to determine the thickness of the cerebral cortex and the X-ray density of the precentral gyrus neurons in males-mesocephalic according to CT-scan. The analysis of CT-scan study results of 55 males masacrans, mesocephalics in age from 22 to 35 years without diseases and traumas of central and peripheral nervous system in anamnesis, with predominance of the right hand (right-handed) was done. Morphometric characteristics of the precentral gyrus the cerebral cortex, were determined at three points: above the upper temporal gyrus, at the level of the middle frontal gyrus and above the cingulate gyrus.

It is found that the maximum width of the precentral gyrus is determined above the upper temporal gyrus. Its minimum value was found above the cingulate gyrus. The largest indicator of the thickness of the cerebral cortex of the precentral gyrus is set at the level of the middle frontal gyrus, the lowest value is noted above the upper temporal gyrus. In the left hemisphere, the maximum X-ray density of neurons in the cerebral cortex of the precentral gyrus is set above the cingulate gyrus. In the right hemisphere, the limiting density of neurons was detected above the upper temporal gyrus. The lowest density of neurons in the cerebral cortex of the precentral gyrus was determined by CT-scan in both hemispheres of the brain at the level of the middle frontal gyrus.

Comparative analysis of the parameters of the width of the precentral gyrus, the thickness of the cerebral cortex and the X-ray density of the precentral gyrus neurons showed a statistically unreliable degree of interhemispheric differences with a tendency to reduce all indicators in the right hemisphere in comparison with the left one.

Keywords: precentral gyrus, cerebral cortex, X-ray density, morphometric characteristics, CT-scan, mesocephalic.

Introduction. The structure of the central nervous system is devoted to many works of both domestic and foreign scientists. Scientists have found that the cerebral cortex, which is a layer of gray matter in different departments has a different thickness. The surface of the crust is characterized by a complex relief, which includes numerous furrows and located between them elevations – convolutions [12, 14]. Of particular interest for various specialties doctors are information about the morphology of the precentral gyrus, since it originates the pyramid pathway responsible for arbitrary movements [13].

The possibilities of using such modern methods as CT-scan or magnetic resonance imaging in the diagnosis of various diseases impose new requirements to the level of knowledge about the parameters and structure of specific anatomical formations, taking into account the sex, age and typological characteristics of the subject [1, 5, 7]. In the scientific literature there is information about the anatomical characteristics and cytoarchitectonics of many areas of the cerebral cortex and cerebellum, taking into account the specific period of postnatal human ontogenesis [2, 11. 15]. At the same time, detailed knowledge of the morphometric features of the precentral gyrus revealed by computed tomography is very scarce and has a fragmentary character.

The aim of the study was to determine the width of the precentral gyrus, to determine the thickness of the cerebral cortex and the X-ray density of the precentral gyrus neurons in males-mesocephalic according to CT-scan.

Materials and methods. The work is based on the analysis of the results of X-ray computer tomographic study of 55 men who underwent examination and treatment in the Department of radiology of the state Autonomous health institution of the Perm region «City clinical hospital №4». The age of the subjects ranged from 22 to 35 years inclusive. The research was approved by the ethical Committee of the E.A.Vagner Perm State Medical University (№10 from 22.11.2017). The examinees had no history of diseases and injuries of the Central and peripheral nervous system, noted the predominance of the right hand (right-handed). All of them agreed to X-ray examination, which was carried out only according to the indications. Transverse-longitudinal (cranial) index of the subjects was 76,6±1,22%.

Review craniography was conducted in the standard projections (frontal and lateral) X-ray Chirana MP 15-B (Slovakia). Craniometrical study included the measurement of the longitudinal and transverse dimensions of the skull and the definition of craniata largest cross-longitudinal index. The study sample was made up objects with a skull of average form – mesocrans, mesocephalic, the value of the cranial index of which is varied in the range from 75,0 to 79,9. The longitudinal and transverse dimensions of the skull were measured at the extreme protruding points on the axial section and in 3D reconstruction mode. CT-scanwas performed on 16-slice apparatus Optima CT 520 (General Electric – GE Healthcare, USA). Scanning was performed by a native with a slice thickness of 5 mm, with subsequent postprocessing reconstructions with a slice thickness of 0.65 mm in the mode of Head