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## FEATURES OF IMMUNE AND METABOLIC PROFILE OF AUTONOMIC DYSFUNCTION ASSOCIATED WITH POLYMORPHISM OF CANDIDATE GENES

**Introduction.** To preserve employable population's health is a most vital task contemporary medicine has to face. Chronic exposure to occupational factors can induce disorders in the immune, humoral, and nervous regulation in workers employed at an oil extraction enterprise and consequently result in work-related pathology. **Our research aim** was to examine peculiarities of immune and metabolome profile of workers who were employed at an oil-extracting enterprise and suffered from vegetative dysfunction that were related to working experience and combined with candidate gene polymorphism. **Materials and methods.** We examined 137 workers employed at an oil-extracting enterprise who had vegetative dysfunction including 66 workers with their working experience at the examined enterprise exceeding 10 years and 71 workers with working experience being shorter than 10 years. Contents of CD3<sup>+</sup>CD95<sup>+</sup>-lymphocytes, TNFR, Bax, and p53 were determined via flow cytometry.

Leukocytes phagocytosis was examined with formalinized ram erythrocytes; contents of IL-6, NO, and homocysteine were determined via ELISA technique. We applied PCR in real time mode to identify SNP of *ApoE*(rs429358), *MTHFR*(rs1801133), *SULT1A1* (rs9282861) genes. **Results.** Immune and metabolome profiles of workers employed at an oil-extracting enterprise with their working experience being longer than 10 years had the following peculiarities: apoptosis, IL-6, and phagocytosis were hyper-activated (Bax, p53, TNFR), and homocysteine contents were elevated as well. These established changes are likely to reflect a pathogenetic relation with T-allele in *MTHFR*(rs1801133) gene which occurred among these workers more frequently than among those whose working experience didn't exceed 10 years ( $\chi^2=4.89$ ;  $p=0.027$ ); this relation may well lead to atherosclerotic vascular disorders. Workers with their working experience being shorter than 10 years had higher NO levels, dopamine production, and greater CD3<sup>+</sup>CD95<sup>+</sup>-marker inhibition than reference levels ( $p<0.05$ ). These established deviations are likely to reflect a pathogenetic relation with the highest frequency of C-allele in *ApoE* (rs429358) gene and A-allele in *SULT1A1* (rs9282861) gene which occurred in them authentically more frequently than among workers with working experience exceeding 10 years ( $\chi^2=4.77-6.99$ ;  $p=0.008-0.028$ ). This, combined with established negative effects, indicates there is a risk that the immune system will be involved (excessive IL-6 and Bax deficiency), disorder in neuro-metabolome regulation will take place (excessive dopamine), and as a result vegetative dysfunction and vascular atherosclerotic changes will occur. Therefore, established imbalance in the immune (excessive apoptosis and phagocytosis), nervous (elevated dopamine), and metabolome (homocysteine hyper-expression and elevated NO due to its unstable forms) regulation that occurs against polymorphism of genes that participate in enzyme detoxification and metabolism such as *MTHFR*(rs1801133), *SULT1A1* (rs9282861), and *ApoE*(rs429358) characterizes peculiarities of immune and metabolome profiles that are related to working experience; workers with such profiles who suffer from vegetative dysfunction run a serious risk of atherosclerosis and hypertension. These peculiarities that are related to working experience and detected in immune and

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metabolome profiles are recommended to be used as markers for identifying early regulatory immune, vegetative, and metabolome disorders in homeostasis regulation in workers employed at an oil-extracting enterprise.

**Key words:** immune status, genetic polymorphism, risk of atherosclerosis and hypertension, working experience at an oil-extracting enterprise, vegetative dysfunction

**Introduction.** Preserving the health of the working-age population, prevention and early diagnosis of occupational diseases is the most important task of modern medicine. Harmful and dangerous chemical (aromatic hydrocarbons), physical (noise intensity, vibration, unfavorable climatic conditions), as well as psychophysiological production factors of oil production enterprise have a negative impact on the health of people employed in oil production [4]. Excessive exposure of occupational groups to these factors over a long period of time might lead to disorders of adaptive reactions, including imbalance of immune, humoral and nervous regulation of physiological functions of the body and, as a result, the development of occupationally pathology [1, 6, 11].

**The aim of the research** was to examine peculiarities of immune and metabolome profile of workers who were employed at an oil-extracting enterprise and suffered from vegetative dysfunction that were related to working experience and combined with candidate gene polymorphism.

**Materials and methods.** The study of features of immune and neurohumoral regulation depending on work experience by employees involved in oil production and having autonomic dysfunction associated with candidate gene polymorphisms (autonomic dysfunction syndrome) was carried out. 137 men having autonomic dysregulation were examined. They were chronically exposed to the production factors of the oil production enterprise during their work. At that, 66 men have more than 10 years of work experience and 71 men have less than 10 years of work experience. The persons examined have the same ethnicity and social status.

The study was conducted as per the standards outlined in the World Medical Association's Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects". All patients signed a voluntary informed consent for the examination.

The content of CD3+CD95+-lymphocytes, tumor necrosis factor receptor TNFR, apoptosis regulator proteins Bax and p53 was determined using flow cytometry using a FACSCalibur instrument (Becton Dickinson, USA).

The content of IL-6, dopamine, ho-

mocysteine and NO were determined by enzyme immunoassay (EIA) using an Elx808 analyzer (BioTek, USA).

The phagocytic activity of peripheral blood leukocytes was studied using formalized ram red blood cells.

Single-nucleotide polymorphisms (SNP) of 3 gene loci were studied by real-time PCR technique using CFX96 Real Time System C1000 Thermal Cycler (BioRAD, Singapore). Genetic material was received from buccal scrapings using a reagent kit AmpliPrime DNA-sorb Form 2 Variant 100 (NextBio LLC, Russia) by a sorbent method. To determine the genetic polymorphism of the examined genes, test following systems (Syntol, Russia) were used: Cys130Arg of apolipoprotein E *ApoE* gene (rs429358); C677T of methyltetrahydrofolate reductase *MTHFR* gene (rs1801133), Arg213His of the sulfotransferase *SULT1A1* gene (rs9282861). The allelic discrimination method in the TaqMan program was applied to determine the human genotype.

For statistical processing of the study results, mathematical statistics methods were implemented using Statistica 10.0 application software package (StatSoft, USA). To assess the data reliability, Student's t-distribution considering the normal distribution of variables in the groups

was used. In the case of deviation from the normal distribution, the nonparametric Mann-Whitney U test was used to compare data.

Calculation of the allele frequency distribution, as well as the  $\chi^2$ , OR odds ratio and its 95% confidence interval (CI) were calculated in Microsoft Excel. Differences between the groups were considered statistically significant at  $p < 0.05$ .

**Results and discussion.** The clinical and laboratory examination of blood samples of employees involved in oil production and having autonomic nervous regulation disorders revealed functional changes in immune and metabolic regulation of physiological functions of the body associated with the work experience (tab. 1).

Inhibition of CD3+CD95+-marker lymphocyte expression level in workers having autonomic disorders is characterized by a significant decrease in its content relative to the reference level regardless of the age of the examined persons ( $p < 0.05$ ).

The detected increase in the content of intracellular molecular inducers and regulators of apoptosis shows hyperactivation of transcription factors of immunocyte apoptosis in employees working in oil production enterprise with a charac-

**Table 1**

**Features of immune and neurohumoral status depending on work experience by employees involved in oil production and having autonomic nervous regulation disorders**

Indicator	Reference range	Employees having >10 years of work experience (n=66)	Employees having <10 years of work experience (n=71)
Bax, %	5 – 9	13.815±1.473*	10.127±1.598
CD3+CD95+-lymphocytes, abs., $10^9/l$	0.63 – 0.97	0.457±0.094**	0.355±0.109**
CD3+CD95+-lymphocytes, %	39 – 49	22.857±2.507**	17.800±2.845**
TNFR, %	1 – 1.5	4.730±0.917**	3.167±1.211**
p53, %	1.2 – 1.8	10.403±2.851**	9.447±1.993**
Absolute phagocytosis, $10^9/cdm$	0.964 – 2.988	2.418±0.190*	2.001±0.141
Percentage of phagocytosis, %	35 – 60	54.682±2.078*	49.333±1.606
Phagocytic number, c.u.	0.8 – 1.2	1.061±0.059*	0.924±0.043
IL-6, pg/ml	0 – 10	1.552±0.115	3.105±0.553*
Dopamine, pg/cc	10 – 100	74.837±3.372	80.247±1.387*
Homocysteine, $\mu\text{mol/l}$	6.26 – 15.01	11.400±2.295*	7.600±0.940
NO, $\mu\text{mol/cdm}$	70.4 – 208.6	136.867±6.871	167.154±8.920*

\* - the differences between the groups are statistically significant ( $p < 0.05$ );

\*\* - differences with the reference level are statistically significant ( $p < 0.05$ )

teristic tendency to increase associated with work experience. Thus, the examined persons having more than 10 years of work experience with autonomic regulation disorders revealed an increased ( $p < 0.05$ ) level of proapoptotic protein Bax relative to the same value in the group of workers having less than 10 years of work experience and the reference level. The content of transcription factor p53 and tumor necrosis factor receptor TNFR significantly ( $p < 0.05$ ) exceeded the established reference levels for these parameters regardless of the work experience of the examined persons, but with higher expression in the group with more than 10 years of work experience.

It was found out that the neuro-metabolomic profile of employees working in oil production enterprise with less than 10 years of work experience and having autonomic dysregulation was associated with increased ( $p < 0.05$ ) dopamine levels relative to the group with more than 10 years of experience. According to the available literature, dopamine affects the processes of proliferation, differentiation, apoptosis, lymphocyte migration and cytokine production [7, 10]. Consequently, activation of dopamine expression and its receptors may cause the development of atherosclerosis and hypertension associated with an imbalance of immune and nervous regulation. Excessive levels of cytokine IL-6 expression shows the development of inflammatory reactions in workers with less than 10 years of experience. The literature provides the information that increased levels of IL-6 and its receptors sIL-6R activate sympathetic nervous regulation with inhibition of parasympathetic mechanisms due to the direct effect on hypothalamic areas, nucleus of solitary pathway of medulla oblongata and baroreceptors of blood vessels ( $p < 0.05$ ) [5, 13].

The detected features of immune and metabolomic regulation depending on work experience by employees involved in oil production and having autonomic

dysfunction are significantly ( $p < 0.05$ ) associated with polymorphic variants of candidate detoxification and metabolism genes: *MTHFR* (rs1801133), *SULT1A1* (rs9282861) and *ApoE* (rs429358) (table. 2). Gene polymorphism is described by the multiplicative model of inheritance ( $\chi^2$  test,  $df = 1$ ).

Changes in the immune and metabolomic profile of workers having more than 10 years of work experience are associated with increased frequency of the T-allele ( $p < 0.05$ ) of *MTHFR* gene (methylene tetrahydrofolate reductase) (rs1801133), which causes inhibition of the expression product activity and, as a result, an increase in homocysteine concentration. Homocysteine has a cytotoxic effect not only on endotheliocytes, but also on neurons when nitric oxide levels decrease under oxidative stress, which causes an increased risk of both neural and cardiovascular pathologies [3, 8, 14]. The results of our study also demonstrate an increase in homocysteine levels against the background of a decrease in NO (table 1) in the group of men with autonomic dysregulation having more than 10 years of work experience ( $p < 0.05$ ).

The gene pool of the group of employees involved in oil production and working less than 10 years and having autonomic dysregulation revealed significantly ( $p < 0.05$ ) increased frequency of the A-allele (69.1%) of the gene of the thermally stable isoform of the detoxification enzyme-sulfotransferase *SULT1A1* (rs9282861) when compared to the group having longer work experience. It is associated with inhibition of drug conjugation reactions, xenobiotics and neurotransmitters, inactivation of estrogen and their metabolites in order to protect against estrogen-mediated mitosis and mutagenesis [12].

In addition, the group of workers having less than 10 years of work experience revealed significantly ( $p < 0.5$ ) increased frequency of the C-allele of the apolipoprotein E *apoe* gene (rs429358) relative

to the group of workers with more than 10 years of work experience. According to the literature, the protein encoded by this allele also has a reduced functional activity, which causes disorders of lipid metabolism, as well as a reduced neuroprotective potential of apolipoprotein E [2, 9]. It creates an additional increased risk for the development of atherosclerosis and hypertension against the background of the established autonomic regulatory disorders.

**Conclusions.** The group of employees involved in oil production and working more than 10 years and having autonomic dysregulation was characterized by hyperactivation of apoptosis processes (p53, TNFR, Bax) and phagocytosis, as well as increased homocysteine levels. The changes identified might reflect a pathogenetic link with the minor T-allele of the *MTHFR* gene (rs1801133), the frequency of which is increased in relation to employees working less than 10 years. In the group of workers having less than 10 years of work experience, excessive levels of nitric oxide (due to its unstable forms), IL-6 against the background of CD3+CD95+ marker deficiency were established relative to the reference values ( $p < 0.05$ ). At the same time, dopamine expression levels were increased relative to workers having high work experience ( $p < 0.05$ ). The revealed abnormalities might reflect a pathogenetic link with the highest frequency of C-allele of *ApoE* gene (rs429358) and A-allele of *SULT1A1* gene (rs9282861), the frequency of which is significantly increased in relation to employees working over 10 years, which proves the participation of the immune system and neurometabolome regulation in the risk of further development of atherosclerosis and hypertension. Thus, the established imbalance of immune (excess of apoptosis and phagocytosis), nervous (excess of dopamine) and metabolic (hyperexpression of homocysteine and excess of NO) regulation along with the polymorphism of genes of detoxification and metabolism enzymes - *MTHFR* (rs1801133), *SULT1A1* (rs9282861) and *ApoE* (rs429358) characterize the features of immune and metabolome regulation depending on work experience by employees having autonomic dysfunction and risk of forming atherosclerosis and hypertension and are recommended to use as marker indicators when identifying the early regulatory immune, autonomic and metabolomic disorders of homeostasis regulation in employees involved in oil production depending on work experience.

Table 2

**Distribution of allele frequencies of candidate genes in employees involved in oil production and having autonomic dysregulation disorders**

Gene / allele		Group of employees having >10 years of work experience (n=66)	Group of employees having <10 years of work experience (n=71)	$\chi^2$	OR (CI 95%)	p
<i>ApoE</i> (rs429358)	T	96.2	86.1	4.77	4.03 (1.06 – 15.02)	0.028
	C	3.8	13.9		0.25 (0.09 – 0.70)	
<i>MTHFR</i> (rs1801133)	C	65.4	81.8	4.89	0.42 (0.19 – 0.92)	0.027
	T	34.6	18.2		2.38 (1.06 – 5.27)	
<i>SULT1A1</i> (rs9282861)	G	52.6	30.9	6.99	0.40 (0.21 – 0.77)	0.008
	A	47.4	69.1		2.48 (1.25 – 4.84)	



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