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ARCTIC MEDICINE

N.V. Zaitseva, M.A. Zemlyanova, Yu.V. Koldibekova, E.V. Peskova, N.I. Bulatova

PROTEIN MARKERS OF NEGATIVE EFFECTS IN CHILDREN UNDER COLD EXPOSURES

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Currently, a promising study is the identification of changes in the level of expressed proteins (omic markers) in the body under the influence of adverse factors, including climatic ones, reflecting the destabilization of homeostasis. The purpose of the study was to identify protein markers of negative effects in children living under the influence of adverse factors of the subarctic climate.

Materials and methods. A study of the proteomic profile of the blood plasma of children was carried out; statistical evaluation of the values of the relative volume of identified protein spots; establishing and evaluating a probable relationship between the change in the relative volume of identified protein spots and the impact of adverse factors of the subarctic climate.

Results and discussion. Under the influence of adverse factors of the subarctic climate in children of the observation group, relative to the indicators in children of the control group, there was a significant change in the volume of proteins (prothrombin, vitronectin, hemoglobin beta subunit, apolipoproteins A1, C-II and C-III, amyloid proteins A-1 and A- 2, P2Y purinoreceptor 12, transthyretin), the expression or decrease in production of which can cause a violation of the cascade of reactions of the blood coagulation system, a change in the development of mature forms of erythrocytes, a violation of the regulation of reverse cholesterol transport, and damage to endothelial cells.

Conclusion. The study made it possible to establish a relationship between the impact of adverse factors of the subarctic climate and the expression of proteins (apolipoprotein C-III, transthyretin, prothrombin, vitronectin, and hemoglobin β-subunit) identified in the blood plasma of children exposed to this effect. The established omic markers make it possible to predict the development of negative effects in the form of impaired hemostasis mechanisms, intracellular cholesterol esterification, insufficient oxygen supply to tissues, and endothelial dysfunction. The obtained results should be used for predicting, early detection and prevention of the development of possible diseases of the cardiovascular system, blood and hematopoietic organs associated with prolonged exposure to natural cold.

Keywords: harmful factors of subarctic climate, omic markers, predicted negative effects, children.

Introduction. In the Russian Federation approximately 40% of all regions are located in the Arctic Zone beyond the Polar circle or are considered to have similarly harsh natural and climatic conditions. These conditions are rather severe since there are considerable temperature fluctuations, long winter, short summer, and high wind speed [6, 13]. Cold is a predominant non-specific factor which is typical for the climate on these territories. Several research works have established that exposure to cold produces certain effects on peripheral skin receptors and epithelium in the upper airways and induces specific thermoregulation reactions of the sympathetic nervous system which prevent overcooling [1, 7, 24]. When a person is exposed to natural cold, his or her body reacts to it, and this reaction involves depletion of some sections in the endogenous antioxidant protection system and excessive lipid peroxidation; also, cold receptors produce their impulses in a different way. All this leads to systemic vascular resistance, impairs vascular permeability and regulation of vascular tone [14]. It should be noted that there are also considerable changes in hemodynamics as a component of thermal homeostasis [12]. Homeostatic systems in the body undergo complicated restructuring, and functional disorders occur in barrier organs (liver, kidneys, spleen, lungs and the immune system) [8]. As a result, there may be a growth in chronic population morbidity and cold is among basic factors causing it.

At present, there is a promising trend in tackling problems related to early detection of health disorders. This trend is identification of changes in levels of expressed proteins (omic markers) in the body under exposure to harmful factors [18, 19, 21], climatic ones included,

FBSI Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, Perm: **ZAITSEVA Nina Vladimirovna** – RAS Academician, MD, Professor, Scientific Director, znv@fcrisk.ru, http://orcid.org/0000-0003-2356-1145; **ZEMLYANOVA Marina Aleksandrovna** – MD, Chief Researcher, Head of the Department, zem@fcrisk.ru, http://orcid.org/0000-0002-8013-9613; **KOLDIBEKOVA Yuliya Vyacheslavovna** – PhD, Senior Researcher, Head of the Laboratory, koldibekova@fcrisk.ru, http://orcid.org/0000-0002-3924-4526; **PESKOVA Ekaterina Vladimirovna** – junior researcher, peskova@fcrisk.ru, https://orcid.org/0000-0002-8050-3059; **BULATOVA Nataliya Ivanovna** – researcher, 1179815@mail.ru, https://orcid.org/0000-0003-3392-9097

which indicate that homeostasis is destabilized. Results produced by a proteomic examination of protein structure of human blood plasma make it possible to assess and predict changes in homeostasis mechanisms at the molecular-cellular level and risks of developing negative effects associated with exposure to extremely cold climate in the Arctic regions.

This research work is a part of the whole cycle of studies conducted by the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies with the focus on identifying omic markers in protein profiles of children under exposure to various environmental factors [4, 5].

The goal of the present work was to identify protein markers of negative effects in children living under exposure to harmful factors of subarctic climate.

Materials and methods. This study was conducted as part of the Industry Research Program of Rospotrebnadzor for 2021-2025. «Scientific substantiation of the national system for ensuring sanitary and epidemiological well-being, managing health risks and improving the quality of life of the population of Russia», paragraph 5.5.3 "Molecular profiling, including based on proteomic and metabolomic analysis, and the study of molecular and cellular mechanisms of involvement of the transformed profile in the pathogenesis of priority non-communicable diseases associated with exposure to environmental factors" (Reg, №. NIOKTR 121032300225-5). We examined 35 blood plasma samples of children living under exposure to natural cold on territories with subarctic climate (the test group) and children who lived on a territory with milder continental climate (the reference group). Both groups were comparable as per age (3-5 years), social and living conditions, absence of any burdened hereditary case history, and minimal or practically absent ambient air pollution with chemicals on the territories where they lived.

The sampling of whole blood from the cubital vein in the morning (on an empty stomach) into a vacutainer for subsequent obtaining of blood plasma from children included in the sample was performed by a procedural nurse on the basis of preschool educational institutions selected for the study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (64th WMA General Assembly, 2013) and approved in the prescribed manner by the Ethics Committee of the Federal Scientific Center for Medical and Preventive Technologies for Public Health Risk Management (Minutes of the meeting № 1 from 06.02.2021). The legal representatives of the children participating in the survey signed a voluntary informed consent to the use of biological material for scientific purposes. The studies conducted did not infringe on the rights, did not jeopardize the well-being of the subjects of the study, and did not harm their health.

Basic data on climatic factors were taken from open databases on climate. We modeled exposure to climatic factors as their complex influence on a person that lasted 11 months each year during 70 years (an average lifetime), excluding 1 month of a vacation which is spent every year beyond a territory where a person lives permanently. The climate was subarctic on the test territory with the average air temperature being -9.4 °C (the cold peak is −50 °C or lower). Temperatures are well below zero for approximately 280 days a year. The climate was continental on the reference territory was continental with the average air temperature being +1.6 °C.

The study was conducted in full conformity with the ethical principles of scientific medical research on human subjects and was approved as per the established procedure by the Committee on biomedical ethics of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies. Legal representatives of all children participating in the research gave their written informed voluntary consent to use of biological materials for scientific purposes.

We identified proteins in blood plasma using analytical technologies for examining proteome with chromate-mass-spectrometry. The procedure involved determining amino acid sequences of fragments of individual proteins as per UniProt freely accessible database with a sampling made as per Homo Sapience taxon. A gene which determined expression of a specific protein was identified using HGNC database of human gene name (https://www.genenames.org/).

We comparatively assessed relative

Table 1

Results produced by identifying protein fractions in blood plasma of the examined children

Protein	Protein stain intensity, int				U-test	Z-test	Validity of differences as per mean values, p≤0.05
	Test group		Reference group				
	$\bar{X}$(SEM)	SD	$\bar{X}$(SEM)	SD			
Hemoglobin subunit β	223.50 (149.69)	473.37	1447.90 (111.83)	353.64	4.000	-3.439	0.001
Apolipoprotein A-I	0.00 (0.00)	0.00	66.50 (27.17)	88.91	30.000	-2.110	0.035
Apolipoprotein C-III	3189.90 (165.72)	524.07	1663.41 (72.10)	228.00	3.000	3.515	0.0004
Apolipoprotein C-II	1504.50 (228.02)	721.07	2326.70 (130.46)	412.54	17.000	-2.457	0.014
Prothrombin	387.30 (151.36)	478.64	1724.60 (20.93)	66.20	6.500	-3.250	0.001
Vitronectin	340.4 (167.93)	531.04	1844.10 (63.03)	199.33	2.000	-3.591	0.0003
Transthyretin	2687.40 (329.60)	1042.30	1541.52 (87.26)	275.95	21.000	2.154	0.031
Serum amyloid protein A-1	711.60 (278.68)	881.26	61.80 (26.38)	196.00	21.000	2.154	0.031

volumes of identified protein stains in children from the test and the reference group as per conventional statistical procedures (simple mean ($\overline{X}$), standard error of mean (SEM) and standard deviation (SD)) using Statistica 10 software package. We applied non-parametric Mann-Whitney U-test (U ≤ Ucr) to determine significance of differences between two independent samplings. The significance level was taken at p ≤ 0.05 when statistical hypotheses were tested.

We identified and assessed a probable correlation between a change in relative volums of identified protein stains and exposure to harmful factors of subarctic climate by calculating odds ratio (OR) and its confidence interval (CI). OR ≥ 1 and the bottom limit of CI≥1 indicated there was an authentic correlation [15].

Results and discussion. Having examined proteomic blood plasma profiles of the examined children from the test group, we identified approximately 30 protein fractions. 8 out of them were authentically different from those identified in blood plasma of children from the reference group as per the intensity of a protein stain (Table 1).

Children from the test group who lived under exposure to harmful factors of subarctic climate had authentically lower volumes of prothrombin (F2 gene), vitronectin (VTN gene) and hemoglobin subunit beta (HBB gene) than children from the reference group, by 4.5 times, 5.4 times and 6.5 times accordingly (p=0.0003-0.001). Reduced production of the identified proteins indicates that there might be certain disorders of the cascade of enzyme responses by the plasma blood clotting system [16, 23] and vascular-thrombocyte homeostasis [25, 26]; there may also be some reduction in development of mature erythrocytes which results in oxygen deficiency in tissues [2, 10].

We detected multi-directional changes in levels of apolipoproteins in blood of children from the test group. Thus, there was a decrease in apolipoprotein A1 (APOA1 gene) and apolipoprotein C-II (APOC2 gene) levels, by 1.5 times, and an increase in apolipoprotein C-III (APOC3 gene) level, by 2.0 times (p=0.0004-0.035) against the reference group. Given the exposure to cold climate, these changes indicate that there is probable deregulation of reverse cholesterol transport from peripheral tissues into blood flow and, subsequently, an increase in some lipid spectrum indicators (total cholesterol, triglycerides) [6, 20]. Besides we established an elevated amyloid protein A-1 level (SAA1 gene) which was by 11.5 times higher in children from the test group against the reference one (p=0.031). We identified amyloid protein A-2 (SAA2 gene) and P2Y purinoceptor 12 (P2RY12 gene) which were not detected in proteome blood plasma profiles of children from the reference group. Amyloid proteins A-1 and A-2 are prone to deposit in interstitial tissues of organized insoluble amyloid fibrils [17]; P2Y purinoceptor 12 is able to activate vasoconstriction of vessels [11]. Progressing accumulation of lipoproteins in blood, expression of amyloid proteins and P2Y purinoceptor 12 can induce damage to endothelial cells resulting in adhesion molecules occurring on their surface. They also stimulate further penetration of monocytes and thrombocytes into sub-endothelial space which is accompanied with endothelial dysfunction [9].

Body overcooling is known to excite and activate the neuroendocrine system; given that, attention should be paid to the transthyretin (TTR gene) concentration which was by 1.7 times higher in blood plasma of children from the test group against the reference one (p=0.031). There are ambiguous opinions about a role transthyretin plays in the body. On one hand, expression of this protein re-

Table 2

Assessment of the correlations between changes in the identified proteins in blood plasma and exposure to harmful factors of subarctic climate

Omic markers of a predicted negative effect	Group	Response to exposure		Odds ratio (OR)	95 % confidence interval (CI)
		yes	no		
Impaired regulation of cholesterol transport					
Decrease in apolipoprotein A-I	test group	9	1	1.00	0.25-6.75
	reference group	1	9		
Increase in apolipoprotein C-III	test group	6	4	13.50	1.20-152.22
	reference group	1	9		
Decrease in apolipoprotein C-II	test group	3	7	3.86	0.33-45.57
	reference group	1	9		
Disorders in blood clotting					
Decrease in prothrombin	test group	7	3	21.0	1.78-248.11
	reference group	1	9		
Decrease in vitronectin	test group	6	4	13.50	1.20-152.22
	reference group	1	9		
Reduced development of mature erythrocytes					
Decrease in hemoglobin subunit beta	test group	8	2	36.00	2.72-476.30
	reference group	1	9		
Deposition of organized insoluble amyloid fibrils in interstitial tissues					
Increase in transthyretin	test group	6	4	13.50	1.20-152.22
	reference group	1	9		
Increase in serum amyloid protein A-1	test group	2	8	2.25	0.17-29.77
	reference group	1	9		

sults in insoluble fibril glycoprotein depositing in intercellular space [11, 22]; on the other hand, some experts consider a possible role transthyretin plays in the peptide neuroprotection by activating the retinol-tiroxin medicated system which implements synaptic plasticity and neurogenesis [3].

We assessed correlations (by calculating odds ratio) between detected changes in the levels of the identified proteins in blood plasma profile under exposure to harmful factors of subarctic climate. The assessment revealed that a possibility of apolipoprotein C-III and transthyretin expression was by 13.5 times higher for children from the test group against the reference one; a possibility of reduced prothroimbin production, by 21.0 times; possibility of reduced vitronectin production, by 13.5 items; and possibility of reduced hemoglobin subunit beta production, by 36.0 times (Table 2).

Predicted negative effects in the examined children are well in line with results produced by scientific research which indicate that there are changes in mechanisms of adaptation restructure developing under exposure to severe climatic conditions in the Arctic regions [2, 6, 10, 12, 13, 14].

Conclusion. Our research established the correlation between exposure to harmful factors of subarctic climate and expression of proteins (apolipoprotein C-III, transthyretin, prothrombin, vitronectin and hemoglobin subunit β) identified in blood plasma of exposed children. These established omic markers give an opportunity to predict developing negative effects including impaired homeostasis and intracellular cholesterol etherification, insufficient oxygen supply to tissues, and endothelial dysfunction. It is advisable to use these research results to predict, detect in due time and prevent various cardiovascular diseases and diseases of blood and blood-making organs associated with long-term exposure to natural cold.

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