TOPICAL ISSUE

Y.D. Kurochkina, M.A. Korolev, E.A. Letyagina, N.E. Banshchikova, A.E. Sizikov, L.A. Bogoderova, Y.B. Ubshaeva, V.O. Omelchenko, A.A. Akimova, A.A. Mullagaliev, O.A. Chumasova, N.A. Ilyina

RISK FACTORS FOR THE DEVELOPMENT OF PNEUMONIA IN PATIENTS WITH IMMUNO-INFLAMMATORY RHEUMATIC DISEASES RECEIVING GIBP DURING COVID-19 PANDEMIC

DOI 10.25789/YMJ.2023.83.15

УДК: 616.72-007.248

Research Institute of Clinical and Experimental Lymphology – Branch of Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences: **KUROCHKINA Yuliya Dmitrievna** – PhD, rheumatology department, research scientist of the laboratory of connective tissue pathology of RICEL, juli_k@bk.ru; ORCID: 0000-0002-7080-777X; **KOROLEV Maxim Aleksandrovich** – MD, deputy director of RICEL, the leading rheumatologist of Novosibirsk region, head of the laboratory of connective tissue pathology of RICEL, kormax@bk.ru; ORCID: 000-0002-4890-0847; **LETYAGINA Elena Alekseevna** - PhD, head of rheumatology department of RICEL, senior researcher at laboratory of connective tissue pathology of RICEL, elena_letyagina@list.ru, ORCID: 0000-0002-6275-2924; **BANSHCHIKOVA Nadezhda Evgenievna** – rheumatologist, junior researcher of the laboratory of connective tissue pathology of RICEL, nadib1990@mail.ru, ORCID:0000-0003-0900-1600; Federal State Budgetary Scientific Institution Research Institute of Fundamental and Clinical Immunology: **SIZIKOV Alexey Eduardovich** – PhD, head of rheumatology department of RIFCI, sizikovae@niikim.ru, , ORCID: 0000-0002-7213-7482; **BOGODEROVA Larisa Aleksandrovna** – PhD, head of rheumatology department of State Novosibirsk Regional Clinical Hospital, bogoderova_okb@mail.ru, ORCID:0000-0002-2570-8035; **UBSHAEVA Yuliya Borisovna** – PhD, rheumatology, research scientist at laboratory of connective tissue pathology of RICEL, leobina@mail.ru, ORCID: 0000-0001-6330-1044; **OMELCHENKO Vitaliy Olegovich** – PhD, rheumatologist, research scientist at laboratory of connective tissue pathology of RICEL, v.o.omelchenko@gmail.com, ORCID: 0000-0001-6606-7185; **AKIMOVA Anna Aleksandrovna** – rheumatologist, junior researcher at laboratory of connective tissue pathology of RICEL, anya-zemtsova@mail.ru, ORCID: 0000-0003-1099-3256; **MULLAGALIEV Arsen Arsenovich** – junior researcher of the laboratory at pharmacological modeling and screening of bioactive molecules of RICEL, arsenm@mail.ru, ORCID: 0000-0002-5213-5658; **CHUMASOVA Oxana Aleksandrovna** – PhD, rheumatologist department of RIFCI, ORCID 0000-0003-3797-6392; **ILYINA Nadezda Aleksandrovna** – rheumatologist department of RIFCI, nadya5481@mail.ru, ORCID 0000-0002-8633-0662

A retrospective analysis of the database of the register of patients with immuno-inflammatory rheumatic diseases receiving treatment with biologic disease-modifying anti-rheumatic drugs in the Novosibirsk region was carried out, which included 318 patients, 94 of whom had indications of pneumonia during the period from 01.04.2020 to 31.12.2020.

There was a statistically significant increase in the risk of developing pneumonia over the age of 60 years and in patients receiving rituximab, while the therapy with TNF-α inhibitors significantly reduced the risk of developing pneumonia.

Keywords: COVID-19, pneumonia, immune-inflammatory rheumatic diseases, biologic disease-modifying anti-rheumatic drugs.

One of the severe manifestations of a new coronavirus infection is pneumonia. Pathological changes in the lungs in patients with COVID-19 are presented in the form of pulmonary edema, diffuse alveolar damage with the formation of hyaline membranes, reactive hyperplasia of type II alveolocytes, protein aggregates, fibrinous exudate, monocytic and macrophage infiltration of the alveolar spaces [19,20]. Immunohistochemical study revealed infiltration of the alveoli with CD68+ cells, CD20+B cells, and CD8+T cells [19]. The pathogenesis of the development of pneumonia is associated with the peculiarities of the virus to bind through the ACE2 receptor, about 83% of which ACE2 is localized on type 2 alveolocytes. After the penetration of the virus into the lung tissue, activation of macrophages and monocytes, activation of Th1 cells that produce GM-CSF and IL-6 occurs. GM-CSF, in turn, activates CD14+CD16+ monocytes to produce IL-6, TNF-α, etc. [18]. The cytokine storm in COVID-19 is characterized by overproduction of IL-6 and TNF-α. SARS-CoV-2 activates NF-κB and interacts with ACE2 on the cell surface, resulting in a decrease in ACE2 expression followed by an increase in AngII. In addition to NF-κB activation, the type 1 angiotensin receptor axis can also induce the expression of TNF-α and the soluble form of IL-6Ra (sIL-6Ra). IL-6 binds to sIL-6R to form the IL-6-sIL-6R complex, which can activate STAT3 [17]. Both NF-kB and STAT3 are able to activate IL-6 production. IL-6 not only binds to sIL-6R but can also bind to the membrane-bound IL-6 receptor (mIL-6R), resulting in a pleiotropic effect on adaptive and innate immune cells and the development of a cytokine storm [16,17].

Interstitial lung disease is often found among patients with immuno-inflammatory rheumatic diseases (IIRD), especially with rheumatoid arthritis, systemic sclerosis, polymyositis, etc., which often requires correction of antirheumatic therapy, as well as the appointment of antifibrotic drugs [3], while the X-ray picture according to computed tomography is similar to changes in the lungs with coronavirus pneumonia [11]. According to D. Galarza-Delgado et al. patients with IIRD who are on biological disease-modifying antirheumatic drugs (bDMARDs) are not susceptible to a more severe course of coronavirus infection, apart from patients treated with rituximab [7]. J. Loarce-Martos et al. also described a more severe course of coronavirus infection with a high risk of bilateral lung injury and mortality among patients treated with rituximab [14]. According to the analysis of the course and outcomes of a new coronavirus infection pursuant to the register of patients receiving bDMARDs, Russian colleagues discovered dependence of the severity of the course of COVID-19 on age, comorbidities [5]. Previously, we also published the results of an anal-

ysis of the outcomes of the course of COVID-19 among patients receiving bDMARDs in the Novosibirsk region, which demonstrated the effect of age on the severity of the disease, as well as the use of rituximab [1].

Despite the data already available to date, the study of the risks of developing a severe course of coronavirus infection in patients on immunosuppression requires further study, in particular, the identification of risk factors for the development of pneumonia in patients with an initially high risk of developing interstitial lung disease.

The purpose of the study is to examine the risk factors for the development of pneumonia in patients with immunoinflammatory rheumatic diseases receiving bDMARDs

Materials and methods. A retrospective analysis of the database of the register of patients with IIRD who received bDMARDs under the Territorial Program of State Guarantees of Free Medical Assistance to Citizens in the Novosibirsk Region was performed.

Patient information included demographics, medical history, disease activity, and therapy received. Data on COVID-19 included clinical manifestations, laboratory data confirming the diagnosis of a new coronavirus infection, and the outcome of the disease.

Statistical analysis. Statistical data processing was carried out on a personal computer using the NumPy, Pandas, SciPy, MatPlotLib and Seaborn libraries for the Python language. Analysis of the joint distribution of binary features was carried out using Fisher's exact test, and the odds ratio (OR) indicator was used as a quantitative assessment of risk change between groups. Comparison of quantitative characteristics was performed using the Mann-Whitney test. The median and the values of the first and second quartiles were used to describe quantitative variables. The description of the qualitative features is given with the indication of the number of patients and their percentage in the corresponding group.

Results. The study included 318 patients with IIRD in the registry of patients receiving bDMARDs, 94 of which had symptoms of a new coronavirus infection (Table 1).

As it can be seen, the majority of the patients are women, while the distribution of diagnoses corresponded to the prevalence of nosologies in the population. The groups of patients who had a new coronavirus infection and those without COVID-19 did not differ in age, duration of the disease, or duration bDMARDs therapy. Most of them received therapy with the anti-B-cell drug rituximab, which is due to the predominance of rheumatoid arthritis nosology in the patient registry; ,TNF-α inhibitors were in second place in terms of frequency of use, followed by IL-17A inhibitors, the smallest number of patients received IL-6 inhibitors and IL12 / 23 axis inhibitors.

The diagnosis of a new coronavirus infection in the group of patients was established according to the then-current "Interim Guidelines: Prevention, Diagnosis and Treatment of a New Coronavirus Infection (COVID-19)" of the Ministry of Health of the Russian Federation, version 6-1 of 28.04.2020.

An analysis of the distribution of age-sex and clinical characteristics of patients by the presence/absence of pneumonia showed that coronavirus pneumonia was more common in women (48%) than in men (37.5% of cases), while pneumonia was more common at an older age (median age was 53 years against 44). Among various nosologies, patients with RA were more likely to develop pneumonia (69% of cases). In the group of patients with proven pneumonia, more than half of the patients received glucocorticoids, while among bDMARDs, in the group of patients treated with rituximab, there was a high incidence of pneumonia (81% of cases).

To analyze the risk factors for the development of pneumonia (Table 2), gender, age of patients, duration of the disease, the diagnosis with which patients were observed, and the therapy received were analyzed. It was shown that age over 60 significantly increased the risk of developing pneumonia (OR = 7.44; p = 0.006). At the same time, out of the analyzed diagnoses, patients with ankylosing spondylitis and psoriatic arthritis have a statistically significantly lower risk of developing pneumonia compared to patients with rheumatoid arthritis (OR=6.05,

Table 1

Clinical characteristics of patients with rheumatic diseases receiving bDMARDs

Parameters	Meaning	
	Without COVID-19	COVID-19
The number of patients, n	224	94
Age, years	49 (39.0; 59.0)	46.5 (38;56)
Sex, n (%)		
Men	78 (34.8)	24 (25.5)
Women	146 (65.2)	70 (74.5)
Diagnosis		
RA	133 (59.4)	49 (52.1)
AS	71 (31.7)	29 (30.9)
PsA	12 (5.4)	12 (12.8)
Other	8 (3.5)	4 (4.3)
Duration of disease, years	15 (7;21)	13 (7; 20)
DMARDs, n (%)		68 (72.3)
Methotrexate	150 (66.9)	42 (44.7)
Sulfasalazine	50 (22)	11 (11.7)
Leflunomide	30 (13.3)	9 (9.6)
Hydroxychloroquine	10 (4.46)	8 (8.5)
Glucocorticoids	10 (4.46)	14 (14.9)
Duration of DMARDs treatment, years	4 (1;7)	3 (1.05;5)
Duration of DMARDs treatment		
Under a year	49 (21.9)	13 (13.8)
Over a year	175 (78.1)	81 (86.2)
bDMARDs		
Rituximab (Acellbia)	121 (54.0)	43 (45.7)
Certolizumab pegol (Cimzia)	32 (14.3)	13 (13.8)
Secukinumab (Cosenthix)	26 (11.6)	11 (11.7)
Adalimumab (Humira)	12 (5.4)	9 (9.6)
Golimumab (Simponi)	15 (6.7)	6 (6.4)
Etanercept (Enbrel)	7 (3.1)	4 (4.3)
Abatacept (Orencia)	1 (0.4)	3 (3.2)
Ixekizumab (Tals)	0 (0)	2 (2.2)
Sarilumab (Kevzara)	0 (0)	1 (1.1)
Olokizumab (Artlegia)	1 (0.4)	1 (1.1)
Ustekinumab (Stelara)	0 (0)	1 (1.1)
Tocilizumab (Actemra)	3 (1.3)	0 (0)
Netakimab (Efleira)	6 (2.7)	0 (0)

p<0.001). Despite a higher incidence of pneumonia among patients treated with glucocorticoids, risk factor analysis did not reveal an effect of hormone intake on the development of pneumonia. At the same time, rituximab therapy significantly increased the risk of developing pneumonia (OR = 15.45, p <0.001), while taking a TNF-α inhibitor reduced the risk of developing pneumonia (OR = 0.1; p <0.001).

Discussion. The results presented in the work confirm the effect of rituximab on the severity of the course of coronavirus infection and associated pneumonia. A number of authors associate the revealed effects with the depletion of B-cells. Earlier studies have shown that iatrogenic depletion of B-lymphocytes increases infectious risks [15]. In the review by E.L. Nasonov [4] the currently existing views on the role of B cells in the course of coronavirus infection were demonstrated. Based on these results, it was concluded that there was a need for a careful approach to the indications for prescribing anti-B-cell drugs during the pandemic of a new coronavirus infection, the need to temporarily cancel treatment if SARS-CoV-2 infection was suspected and the disease was developing.

Another important issue related to the use of rituximab in COVID-19 pandemic is the vaccination of patients with IIRD. According to the current recommendations, patients with IIRD should be vaccinated against COVID-19 in order to minimize the high risks of a severe course of the disease [2,13]. The question of the effectiveness of vaccination in patients who have already received rituximab and have B-cell depletion is relevant. Michael Markus Bonelli et al. showed that in patients treated with rituximab, there was a decrease in the humoral response with a preserved T-cell response [22], while therapy with TNF-α inhibitors had practically no effect on antibody production [6]. Currently, there are data on the possibility of using monoclonal antibodies to SARS-COV-2 to reduce the risk of severe coronavirus infection in immunocompromised patients [21].

Age is an undeniable risk factor for severe COVID-19 and pneumonia. Fei Zhou et al. showed that the mortality of patients with severe pneumonia and respiratory distress syndrome occurred in an older age group and is a risk factor associated with in-hospital mortality [9].

As it is known, therapy with TNF-α inhibitors in patients with IIRD is associated with infectious risks. However, data from various studies show that therapy with TNF-α inhibitors in patients with inflammatory joint diseases does not increase, but reduces the risk of a severe course of coronavirus infection [8,10,12], which is consistent with our results.

Over the past three years of the pandemic, the SARS-CoV-2 virus has mutated, which affected not only the contagiousness, but also the severity of clinical manifestations. Currently, there is a lower incidence of severe cases and a decrease in mortality in the population, however, whether the susceptibility, as well as the severity of the course of COVID-19, has changed in patients with IIRD receiving bDMARDs, requires further study.

Conclusion. Rituximab therapy during the COVID-19 pandemic significantly increases the risk of a severe course of a new coronavirus infection, the development of pneumonia, and the likelihood of death. Treatment with TNF-α inhibitors reduces the risk of developing pneumonia associated with SARS-COV-2.

All patients treated with rituximab are recommended to be vaccinated, as well as to receive virus-neutralizing monoclonal antibodies to SARS-COV-2.

The work was carried out within the framework of RICEL Subject No. FWNR-2023-0009.

Table 2

Analysis of the qualitative characteristics of patients as potential risk factors for pneumonia in COVID-19

Parameters	The presence of feature, N1 / N2	The absence of feature, N1 / N2	OR	p
Sex: male	9 / 15	36 / 33	0.55	p = 0.244
Age > 60	11 / 2	34 / 46	7.44	p = 0.006
Daignosis RA AS psA	 33 / 15 8 / 21 2 / 10	 12 / 33 37 / 27 43 / 38	 6.05 0.28 0.18	 p < 0.001 p = 0.008 p = 0.028
Duration of the disease (years) > 5	36 / 39	9 / 9	0.92	p = 1.000
DMARDs	36 / 31	8 / 15	2.18	p = 0.149
Glucocorticoids	9 / 5	35 / 41	2.11	p = 0.253
Inhibitors of TNF-α	5 / 27	40 / 21	0.10	p < 0.001
Inhibitors of IL-6	0 / 2	45 / 46	0.00	p = 0.495
Inhibitors of IL-17	4 / 9	41 / 39	0.42	p = 0.235
Anti-B-cells therapy	34 / 8	11 / 40	15.45	p < 0.001
Anti-T-cells therapy	1 / 2	44 / 46	0.52	p = 1.000

* N1 – pneumonia, N2 – without pneumonia, OR – odds ratio.

Reference

1. Korolev M.A. [et al.]. Immunovospalitel'nye revmaticheskie zabolevaniya i COVID-19: analiz klinicheskih iskhodov po dannym registra pacientov Novosibirskoj oblasti, poluchayushchih terapiyu genno-inzhenernymi biologicheskimi preparatami [Immune-inflammatory rheumatic diseases and COVID-19: analysis of clinical outcomes according to the data of the register of patients of the Novosibirsk region receiving therapy with genetically engineered biological drugs]. Terapevtich. arhiv [Ter. Arkh. 2022; 94(5):636–641 (In Russ.).] doi: 10.26442/00403660.2022.05.201502

2. Nasonov E.L. [et al.]. Koronavirusnaya bolezn' 2019 (COVID-19) i immunovospalitel'nye revmaticheskie zabolevaniya. Rekomendacii Obshcherossijskoj obshchestvennoj organizacii «Associaciya revmatologov Rossii» [Coronavirus Disease 2019 (COVID-19) and Immune-mediated Rheumatic Diseases. Recommendations of the Association of Rheumatologists of Russia]. Nauch.-praktich. Revmatologiya [Rheumatol. Sci. Pract. 2021; 59(3): 239–254 (In Russ.).] https://doi.org/10.47360/1995-4484-2021-239-254

3. Nasonov EL, Anan'eva LP, Avdeev SN. Interstitial'nye zabolevaniya legkih pri revmatoidnom artrite: mul'tidisciplinarnaya problema revmatologii i pul'monologii [Interstitial lung disease in rheumatoid arthritis: A multidisciplinary problem in rheumatology and pulmonology]. Ibid. 2022; 60 (6): 517–534 (In Russ.).] doi: 10.47360/1995-4484-2022-1

4. Nasonov E.L., Avdeeva A.S. Depleciya V-kletok pri immunovospalitel'nyh revmaticheskih zabolevaniyah i koronavirusnaya bolezn' 2019 (COVID-19) [B cell depletion in immune-mediated rheumatic diseases and coronavirus disease 2019 (COVID-19)]. Ibid. 2021; 59 (4): 384–393 (In Russ.).] https://doi.org/10.47360/1995-4484-2021-384-393

5. Nasonov E.L. [et al.]. Techenie i iskhody COVID-19 u pacientov s immunovospalitel'nymi revmaticheskimi zabolevaniyami: predvaritel'nye dannye registra NIIR/ARR-COVID-19 i obzor literatury [Course and outcomes of COVID-19 in patients with immunoinflammatory rheumatic diseases: Preliminary data from the NIIR/APP-COVID-19 registry and literature review. Ibid.

2021b; 59 (6): 666–675 (In Russ.).] https://doi.org/10.47360/1995-4484-2021-666-675

6. Boyarsky B.J. [et al.]. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. Ann. Rheum. Dis. 2021; 80(8): 1098–1099. doi/10.1136/annrheumdis-2021-220289

7. Galarza-Delgado D.Á [et al.] Characteristics and evolution of 38 patients with rheumatic diseases and COVID-19 under DMARD therapy. Clin. Rheumatol. 2021; 40 (3): 1197–1199. Available from: http://link.springer.com/10.1007/s10067-020-05510-9

8. Gianfrancesco M [et al.] Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann. Rheum. Dis. 2020; 79(7): 859–866. doi/10.1136/annrheumdis-2020-217871

9. Zhou F. [et al.] Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020a; 395 (10229): 1054–1062. DOI:https://doi.org/10.1016/S0140-6736(20)30566-3

10. Monti S [et al.]. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann. Rheum. Dis. 2020; 79(5): 667–668. doi/10.1136/annrheumdis-2020-217424

11. Eslambolchi A [et al.]. Coronavirus disease 2019 (COVID-19) in patients with systemic autoimmune diseases or vasculitis: radiologic presentation. J. Thromb. Thrombolysis. 2021; 51(2): 339–348. Available from: https://link.springer.com/10.1007/s11239-020-02289-z

12. Haberman R.H. [et al.]. COVID-19 in Patients With Inflammatory Arthritis: A Prospective Study on the Effects of Comorbidities and Disease-Modifying Antirheumatic Drugs on Clinical Outcomes. Arthritis Rheumatol. 2020;72 (12): 1981–1989. doi/10.1002/art.41456

13. Landewé R.B.M [et al.]. EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update. Ann. Rheum. Dis. 2022. C. annrheumdis-2021-222006. doi/10.1136/annrheumdis-2021-222006

14. Loarce-Martos J [et al.]. High rates of severe disease and death due to SARS-CoV-2 infection in rheumatic disease patients treated with rituximab: a descriptive study/ Rheumatol. Int. 2020; 40(12): 2015–2021. Available from: http://link.springer.com/10.1007/s00296-020-04699-x

15. Vollenhoven R.F. van [et al. Longterm Safety of Patients Receiving Rituximab in Rheumatoid Arthritis Clinical Trials. J. Rheumatol. 2010;37(3): 558–567. doi/10.3899/jrheum.090856

16. Moore J.B., June C.H. Cytokine release syndrome in severe COVID-19 // Science (80-). 2020; 368(6490): 473–474. doi/10.1126/science.abb8925

17. Murakami M., Kamimura D., Hirano T. Pleiotropy and Specificity: Insights from the Interleukin 6 Family of Cytokines. Immunity. 2019;50(4): 812–831. Available from: https://linkinghub.elsevier.com/retrieve/pii/S107476131930144X

18. Zhou Y. [et al.]. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. Natl. Sci. Rev. 2020b; 7(6): 998–1002. doi: 10.1093/nsr/nwaa041

19.Yao X.-H. [et al.]. Pathological evidence for residual SARS-CoV-2 in pulmonary tissues of a ready-for-discharge patient . Cell Res. 2020; 30(6): 541–543. DOI: 10.1038/s41422-020-0318-5

20. Xu Z. [et al.]. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 2020; 8(4): 420–422. DOI: 10.1016/S2213-2600(20)30076-X

21. Nguyen Y.[et al.] Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) for COVID-19 among 1112 severely immunocompromised patients. Clinical Microbiology and Infection. 2022; 28:1654.e1e1654.e4. https://doi.org/10.1016/j.cmi.2022.07.015

22. Bonelli M.M [et al.]. SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response. Ann. Rheum. Dis. 2021; 80(10): 1355–1356. doi/10.1136/annrheumdis-2021-220408

N.V. Zaitseva, O.V. Dolgikh, A.A. Subbotina, A.V. Yaroma

POLYMORPHISM OF THE MICROSOMAL EPOXIDE HYDROLASE *EPHX1* GENE (RS1051740) IN FREQUENTLY ILL CHILDREN FROM AN INDUSTRIAL AREA IN SOUTHERN SIBERIA

DOI 10.25789/YMJ.2023.83.16

УДК: 575.164

The aim of the study was to analyze frequency of the EPHX1 gene polymorphism (rs1051740) associated with diseases of the upper airways and elevated manganese levels in biological media of children from an industrial area located in the Southern Siberia.

Materials and methods. We examined children aged 4-7 years who permanently lived in an industrial area in the Southern Siberia. It was a monotown with its economy dominated by a large non-ferrous metallurgy plant. The test group was made of 60 children who were often sick (more than 6 times a year) for a long time. The reference group included 39 conditionally healthy children with manganese levels in their blood being within the reference range. We identified frequency of polymorphism of the microsomal epoxide hydrolase EPHX1 gene (rs1051740) and the cytochrome C level using PCR and ELISA accordingly. The statistical significance was taken at p<0,05.

Results and discussion. Average manganese levels were 1,8 times significantly higher in blood of the children from the test group than in the reference one. We established statistically significant authentic differences in frequencies of the EPHX1 gene genotypes and alleles (rs1051740) between the test and reference groups (the C/C genotype was 3,2 times more frequent; the C allele, 1,5 times, p<0,05). Cytochrome C levels were 2,2 times lower in blood serum in the test group against the reference one.

Conclusions. The study established several peculiarities in children who often had diseases of the upper air ways (the test group). They had elevated manganese levels in their blood, higher than its safe level; the serum cytochrome C level was lower in them; they more frequently had the C/C genotype (OR=4,05, 95% CI=1,26-13,05) and the C allele (OR=1,98, 95% CI=1,09-3,60) of the EPHX1 gene (rs1051740). Many authors believe polymorphism of this gene to be a risk factor able to cause respiratory

ZAITSEVA Nina Vladimirovna – MD, Scientific Director of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, znv@fcrisk.ru. ORCID: 0000-0003-2356-1145; **DOLGIKH Oleg Vladimirovich** – MD, head of the Department of Immunobiological Diagnostics, Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, oleg@fcrisk.ru. ORCID:0000-0003-4860-3145; **SUBBOTINA Alena Aleksandrovna** – junior researcher at the Immunogenetics laboratory of the Department of Immunobiological Diagnostics, the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, alena-osa@bk.ru. ORCID: 0000-0002-3579-4125; **YAROMA Alesya Vyacheslavovna** – junior researcher at the Cellular Diagnostic Laboratory of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, lady.yaroma@mail.ru. ORCID:0000-0002-0932-3063.