ИНФЕКЦИОННЫЕ БОЛЕЗНИ
INFECTIOUS DISEASES

LIPID PEROXIDATION – ANTIOXIDANT DEFENSE SYSTEM IN CHILDREN WITH SEASONAL INFLUENZA

Kazantseva E.D.,
Darenskaya M.A.,
Rychkova L.V.,
Petrova A.G.,
Semenova N.V.,
Kurashova N.A.,
Grebenkina L.A.,
Kolesnikova L.I.

Scientific Centre for Family Health and Human Reproduction Problems (Timiryazeva str. 16, Irkutsk 664003, Russian Federation)

Corresponding author:
Ekaterina D. Kazantseva,
e-mail: kat.smile7@yandex.ru

ABSTRACT

Introduction. *Influenza remains a serious viral infection in children and has consequences for the organism.*
The aim of the study. *To analyze the lipid peroxidation products and antioxidant defense (AOD) components level in children of two age groups with seasonal influenza. Materials and methods. We examined 141 children aged from 1 month to 6 years with a diagnosis of influenza (subgroup 1 – 1 month – 2.11 years (n = 78); subgroup 2 – 3–6 years (n = 63)), 47 children of control group (subgroup 3 – 1 month – 2.11 years (n = 17); subgroup 4 – 3–6 years (n = 30)). Spectrophotometric, fluorometric and statistical methods were used.*
Results. *In subgroup 1 of children with influenza, there were higher levels of compounds with double bonds ($p = 0.001$), conjugated dienes (CDs) ($p < 0.0001$), ketodienes and conjugated trienes (KD and CT) ($p = 0.004$); in subgroup 2 of children with influenza – increased values of CDs ($p < 0.0001$), KD and CT ($p < 0.0001$) and thiobarbituric acid reactants ($p < 0.0001$) compared to the control. The AOD system in subgroup 1 was characterized by a decrease in the level of α-tocopherol ($p < 0.0001$), retinol ($p < 0.0001$) and higher oxidized glutathione (GSSG) values ($p = 0.002$) compared to the control. Children of subgroup 2 had lower values of the level of α-tocopherol ($p < 0.001$), retinol ($p = 0.012$) and total antioxidant activity ($p < 0.0001$) and higher values of GSSG ($p = 0.035$) compared to the control.*
Conclusion. *In children with influenza, regardless of age, there is a higher level of production of lipid peroxidation indicators, a lack of fat-soluble vitamins and higher values of oxidized glutathione than in healthy children.*

Key words: *influenza, children, lipid peroxidation, antioxidant defense*

Received: 14.03.2024
Accepted: 10.06.2024
Published: 15.07.2024

For citation: Kazantseva E.D., Darenskaya M.A., Rychkova L.V., Petrova A.G., Semenova N.V., Kurashova N.A., Grebenkina L.A., Kolesnikova L.I. Lipid peroxidation – antioxidant defense system in children with seasonal influenza. *Acta biomedica scientifica*. 2024; 9(3): 95-101. doi: 10.29413/ABS.2024-9.3.9

ПЕРЕКИСНОЕ ОКИСЛЕНИЕ ЛИПИДОВ – СИСТЕМА АНТИОКСИДАНТНОЙ ЗАЩИТЫ У ДЕТЕЙ С СЕЗОННЫМ ГРИППОМ

Казанцева Е.Д.,
Даренская М.А.,
Рычкова Л.В.,
Петрова А.Г.,
Семёнова Н.В.,
Курашова Н.А.,
Гребенкина Л.А.,
Колесникова Л.И.

ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека» (664003, г. Иркутск, ул. Тимирязева, 16, Россия)

Автор, ответственный за переписку:
Казанцева Екатерина Дмитриевна,
e-mail: kat.smile7@yandex.ru

РЕЗЮМЕ

Введение. *Грипп остаётся серьёзной вирусной инфекцией у детей и имеет последствия для здоровья.*

Цель исследования. *Проанализировать уровень продуктов перекисного окисления липидов и компонентов антиоксидантной защиты (АОЗ) у детей двух возрастных групп, больных сезонным гриппом.*

Материалы и методы. *Обследован 141 ребёнок в возрасте от 1 месяца до 6 лет с диагнозом грипп (1-я подгруппа – от 1 месяца до 2,11 года (n = 78); 2-я подгруппа – 3–6 лет (n = 63)); 47 детей контрольной группы (3-я подгруппа – от 1 месяца до 2,11 года (n = 17); 4-я подгруппа – 3–6 лет (n = 30)). Использовались спектрофотометрические, флуориметрические и статистические методы.*

Результаты. *В 1-й подгруппе детей с гриппом отмечались более высокие уровни соединений с двойными связями (p = 0,001), диеновых конъюгатов (ДК) (p < 0,0001), кетодиенов и сопряжённых триенов (КД и СТ) (p = 0,004); во 2-й подгруппе детей с гриппом – повышенные значения ДК (p < 0,0001), КД и СТ (p < 0,0001) и ТБК-активных продуктов (p < 0,0001) в сравнении с контролем. Система АОЗ в 1-й подгруппе характеризовалась снижением уровня α-токоферола (p < 0,0001), ретинола (p < 0,0001) и более высокими значениями окисленного глутатиона (GSSG) (p = 0,002) по отношению к контролю. У детей 2-й подгруппы отмечались более низкие значения уровня α-токоферола (p < 0,001), ретинола (p = 0,012), общей антиокислительной активности (p < 0,0001) и повышенные значения GSSG (p = 0,035) в сравнении с контролем.*

Заключение. *У детей при гриппе независимо от возраста отмечаются более высокий, чем у здоровых детей, уровень продуктов липопероксидации, недостаток жирорастворимых витаминов и повышенные значения окисленного глутатиона.*

Ключевые слова: *грипп, дети, перекисное окисление липидов, антиоксидантная защита*

Статья получена: 14.03.2024
Статья принята: 10.06.2024
Статья опубликована: 15.07.2024

Для цитирования: Казанцева Е.Д., Даренская М.А., Рычкова Л.В., Петрова А.Г., Семёнова Н.В., Курашова Н.А., Гребенкина Л.А., Колесникова Л.И. Перекисное окисление липидов – система антиоксидантной защиты у детей с сезонным гриппом. *Acta biomedica scientifica*. 2024; 9(3): 95-101. doi: 10.29413/ABS.2024-9.3.9

ABBREVIATIONS

AOD – antioxidant defence
CDs – conjugated dienes
DB – double bounds
GSH – reduced glutathione
GSSG – oxidized glutathione
KD and CT – ketodienes and conjugated trienes
LPO – lipid peroxidation
OS – oxidative stress
SB – Schiff basis
SOD – superoxide dismutase
TAA – total antioxidant activity
TBARs – thiobarbituric acid reactants

INTRODUCTION

Influenza remains a pressing acute respiratory viral infection, which causes significant social and economic damage to public health [1]. Influenza and influenza-like infections are comparable in scale of damage to traumas, cardiovascular diseases and malignant neoplasms [2]. The influenza virus is characterized by seasonal circulation; small children, the elderly, people with weakened immune system and people with chronic diseases are at risk and have a high susceptibility to this disease [3]. The number of sick children during the epidemic period exceeds 30 %, the probability of illness and the risk of severe course in children is 1.5–3 times higher than in adults [4]. The influenza virus has significant genetic variability, which reduces the effectiveness of existing vaccines and limits the therapeutic possibilities due to the emergence of new strains resistant to standard therapy [3]. The emergence of a new coronavirus infection caused by SARS-CoV-2 requires new diagnostic and therapeutic options, especially in risk groups, since influenza viruses and SARS-CoV-2 are both RNA viruses [2]. In the pathogenetic mechanisms of the infectious process during influenza, of great importance is the nonspecific defense system: lipid peroxidation-antioxidant defense (LPO-AOD) [5].

The role of LPO has been proven in the phagocytosis and destruction of microorganisms, in the metabolism of some xenobiotics, and in the synthesis of some biologically active substances, in particular prostaglandins [6–8]. Because hydroperoxides act as primary stable products in the oxidation of unsaturated fatty acids of phospholipids, this process is called peroxidation. Subsequently, peroxidative degradation of phospholipid molecules occurs, which changes the conformation of the cell membrane and lipoproteins [9]. Excessive synthesis of lipid peroxidation products is prevented by the antioxidant defense system, the main elements of which are antioxidants – substances that inhibit or reduce the intensity of free radical oxidation, neutralizing free radicals, exchanging their hydrogen atom for the oxygen of free radicals [10, 11]. Currently, the study of this process is very relevant and the role of oxidative stress in children of different ages and in various pathological conditions (arterial hypertension, chronic gastroduodenitis, influenza, cholelithiasis, pyelonephritis, metabolic syndrome, type 1 diabetes mellitus) has been proven [12, 13]. Despite the available research, there are very little data on changes in this system in children with influenza in a comparative age aspect.

THE AIM OF THE STUDY

To analyze the lipid peroxidation products and antioxidant defense components level in children of two age groups with seasonal influenza.

MATERIALS AND METHODS

We examined 141 children diagnosed with influenza who were hospitalized at the Irkutsk Regional Infectious Diseases Clinical Hospital from 2018 to 2019; the average age of the patients was 2.87 ± 0.9 years. In the control group (n = 47), the average age of patients was 3.13 ± 1.1 years. In the main group, patients were divided into subgroups: subgroup 1 – 1 month – 2.11 years (n = 78); subgroup 2 – 3–6 years (n = 63)), control group: subgroup 3 – 1 month – 2.11 years (n = 17), subgroup 4 – 3–6 years (n = 30).

When working with case histories, the following were assessed: gender, age of a child, duration of hospitalization, main diagnosis, concomitant diagnosis, presence of complications, nature and duration of the main clinical symptoms, general and biochemical blood tests, verification of the influenza virus by polymerase chain reaction.

Gender structure of patients with influenza: 70 (52 %) boys and 64 (48 %) girls; average age – 3 years. In the structure of influenza incidence, influenza A (H1N-1sw2009) serotype predominated – in 76 % of cases, influenza A (H3N2) made 16 %. In the structure of concomitant diagnoses, a significant place belongs to acute intestinal infection – 16 % (of rotavirus and noravirus etiology), atopic dermatitis was notes in 2 % of cases, hypochromic anemia – in 6 %, enterobiasis was observed in isolated cases.

The structure of complications of the underlying disease: acetonemic vomiting syndrome or ketoacidosis syndrome was observed in 12 % of cases, pneumonia was detected in 16 %, obstructive bronchitis – in 2 %. The average length of hospitalization was 5 ± 1.6 days.

The clinical picture of seasonal influenza had the following characteristics: 66 % of children had a runny nose, 84 % had dry cough, 92 % had fever, and 38 % of children had complaints of intoxication. Apathy and drowsiness were observed in 44 % of patients, weakness was observed in 34 %, decreased appetite in 26 %, headaches bothered 8 % of children, pain in muscles and joints was not observed in anyone. Sore throat and pain when swallowing were noted by 6 % of children, abdominal pain and diarrhea were observed in 8 % of children, vomiting – in 28 %, convulsions – in 4 %, ear pain and dizziness – in 1 % of children.

The nature of rhinitis in 72 % of cases was mucous, the duration of the runny nose was 5 ± 2.48 days. The nature of the cough in 84 % of cases was dry; 6 % of children had wet cough, duration – 5 ± 1.5 days. The median body temperature during fever was 38.5 ± 0.68 °C, the duration of fever was 2 ± 1.45 days. Pharyngeal hyperemia was observed in 96 % of cases.

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association (1964, ed. 2013) and approved by the Biomedical Ethics Committee at the Scientific Centre for Family Health and Human Reproduction Problems (Extract from meeting No. 8.4 of November 2, 2018).

The research materials were plasma and serum. The S-monovette dipotassium ethylene diamine tetraacetic acid (K3-EDTA) blood collection system (Sarstedt, Germany) was used for venous blood collection (10 mL). The analysis was conducted after overnight rest of subjects, blood was taken on an empty stomach, between 8.00 and 9.00 a. m. Immediately after collection, blood was centrifuged at 1500× g for 10 min to separate the plasma from the erythrocytes. Plasma was taken, and the erythrocytes were washed three times in cold saline solution (0.9 % NaCl, w/v). Then, the erythrocytes were hemolyzed by adding 9 volumes of cold 50 mM phosphate buffer of pH = 7.4 (v:v). Samples were kept frozen at the temperature of –40 °C until use.

The intensity of the lipid peroxidation processes was assessed by the content of unsaturated double bonds (DB), primary products – conjugated dienes (CDs), and secondary – ketodienes and conjugated trienes (KD and CT) products by the method of I.A. Volchegorskiy et al. (1989) [14], based on the intensive absorption of conjugated diene structures by lipid hydroperoxides in the range 220, 232 and 278 nm. The content of end products – thiobarbituric acid reactive substances (TBARs) and Schiff basis (SB) – was determined in the reaction with thiobarbituric acid in the range 532 and 440 nm using the fluorimetric method of V.B. Gavrilov et al. (1987) [15]. Total antioxidant activity (TAA) was evaluated by the method of G.I. Klebanov et al. (1988) [16]. To evaluate TAA, a model system, which is a lipoprotein suspension of chicken egg yolk that allows to evaluate the ability of blood serum to inhibit the accumulation of TBARs in suspension, was used. LPO was induced by adding $FeSO_4*7H_2O$. The content of reduced and oxidized glutathione (GSH and GSSG) was determined by P.J. Hissin, R. Hilf (1976) [17], the activity of superoxide dismutase (SOD) was measured using the method of H.P. Misra, I. Fridovich (1972) [18]. Concentrations of α-tocopherol and retinol were determined using the method of R.Ch. Chernyauskene et al. (1984) [19]. The method provides for the removal of substances that prevent determination by saponification of samples in the presence of large amounts of ascorbic acid and extraction of unsaponifiable lipids with hexane, followed by fluorometric determination of the content of α-tocopherol and retinol. At this, α-tocopherol has intense fluorescence with maximum of excitation at λ = 294 nm and radiation at λ = 330 nm; retinol at λ = 335 and λ = 460 nm.

Plasma was analyzed to determine the levels of lipid peroxidation products (DB, CDs, KD and CT, TBARs, SB) and antioxidant defense factors (TAA, α-tocopherol, retinol). SOD, GSH, and GSSG were estimated in erythrocytes.

The measurements were carried out using a spectrophotometer SF-2000 (Russia), a spectrofluorophotometer BTS-350 (Spain) and fluorate 02 ABFF-T (Russia).

The work was carried out using the equipment of the Center for the Development of Advanced Personalized Health Technologies of the Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk.

To analyze the obtained data, the statistical package Statistica 10.0 (StatSoft Inc., USA) was used. To determine the proximity to the normal law of distribution of quantitative characteristics, a visual-graphical method and Kolmogorov – Smirnov agreement criteria with the Lilliefors and Shapiro – Wilk correction were used. Equality of common variances was tested using Fisher's test (F-test). The nonparametric Mann – Whitney test was used to analyze intergroup differences for independent samples. The critical significance level was set at 5 % (0.05).

RESULTS AND DISCUSSION

The obtained data are presented in Table 1.

Data analysis in children with seasonal influenza in age group 1 showed statistically significantly higher values of compounds with unsaturated DB, CDs, KD and CT compared to the corresponding control (Table 1).

In the group of children of age group 2 with influenza, the differences concerned increased values of CDs, KD and CT and TBARs (Table 1).

The AOD system in age group 1 of children with influenza was characterized by lower levels of α-tocopherol, retinol and higher values of GSSG (Table 1).

Children of age group 2 had lower values of α-tocopherol, retinol, total AOA and higher values of GSSG (Table 1).

No statistically significant differences were obtained between different age groups of children with influenza.

In the formation of homeostasis of any living organisms, LPO-AOP processes play an important role, which has been proven by numerous scientific studies [7, 20]. In a healthy body, two processes occur in parallel in all cells and membranes: on the one hand, it is LPO and the formation of free radical metabolic products; on the other hand, it is a powerful antioxidant defense [20]. Hyperactivation of these processes leads to the formation of oxidative stress, which is of significant importance in the pathogenesis of infectious diseases [21]. LPO metabolites lead to proliferation of cells of the immune system, accumulation of neutrophils at the site of inflammation, change surface receptors in macrophages, and increase the expression of adhesion molecules on endothelial cells [7]. The death of the infectious agent in the pathogenesis of inflammatory reactions is possible only if one's own tissues are damaged at the site of injury. As a result of free radical oxidation, damage to mitochondrial membranes and nuclear structures of cells occurs, this in turn leads to the destruction of blood vessels and barrier mechanisms at the cellular level, resulting in the development of a disease with in-

TABLE 1

LEVELS OF LPO PRODUCTS AND AOD COMPONENTS IN CHILDREN OF TWO AGE GROUPS WITH SEASONAL INFLUENZA, ME (Q1; Q3)

Parameters	Control (1 month – 2.11 years) (n = 17)	Influenza (1 month – 2.11 years) (n = 78)	Control (3–6 years) (n = 30)	Influenza (3–6 years) (n = 63)	p
	1	2	3	4	
DB, units	1.54 (1.22; 1.80)	2.46 (1.68; 3.18)	1.94 (1.68; 2.18)	2.23 (1.48; 3.01)	$p_{1-2} = 0{,}001$
CDs, μmol/L	1.19 (0.96; 1.38)	2.30 (1.68; 3.25)	1.00 (0.82; 1.38)	2.33 (1.44; 3.12)	$p_{1-2} < 0{,}0001$ $p_{3-4} < 0{,}0001$
KD and CT, units	0.47 (0.28; 0.80)	0.76 (0.48; 1.36)	0.37 (0.24; 0.66)	0.74 (0.42; 1.14)	$p_{1-2} = 0{,}004$ $p_{3-4} < 0{,}0001$
TBARs, μmol/L	1.03 (0.92; 1.33)	1.47 (0.83; 2.01)	0.82 (0.62; 1.13)	1.55 (1.08; 2.06)	$p_{3-4} < 0{,}0001$
SB, units	0.04 (0.03; 0.05)	0.05 (0.03; 0.09)	0.05 (0.04; 0.06)	0.07 (0.03; 0.12)	
retinol, μmol/L	1.75 (1.63; 1.97)	1.23 (1.08; 1.58)	1.32 (1.14; 1.88)	1.22 (0.95; 1.51)	$p_{1-2} < 0{,}0001$ $p_{3-4} = 0{,}012$
α-tocopherol, μmol/L	10.00 (9.47; 11.74)	6.28 (5.30; 7.46)	8.67 (6.35; 10.22)	6.27 (5.05; 7.47)	$p_{1-2} < 0{,}0001$ $p_{3-4} < 0{,}001$
TAA, units	16.43 (8.87; 26.28)	12.15 (8.62; 15.94)	18.01 (14.68; 26.81)	12.20 (8.27; 15.76)	$p_{3-4} < 0{,}0001$
GSSG, mmol/L	1.86 (1.56; 2.22)	2.33 (2.23; 2.57)	1.96 (1.69; 2.46)	2.32 (2.12; 2.55)	$p_{1-2} = 0{,}002$ $p_{3-4} = 0{,}035$
GSH, mmol/L	2.42 (2.11; 2.65)	2.34 (2.24; 2.52)	2.52 (2.24; 2.66)	2.33 (2.27; 2.58)	
SOD activity, units	1.56 (1.55; 1.60)	1.61 (1.57; 1.68)	1.56 (1.52; 1.59)	1.60 (1.55; 1.64)	

Note. p – statistically significant differences between groups with influenza and control groups.

flammatory, toxic and autoimmune mechanisms in pathogenesis [22, 23]. The synthesis of various other metabolites leads to persistent changes in the composition of biomembranes, the development of a serious imbalance in the LPO-AOD system, and they further have a damaging effect on healthy cells of the body.

We have shown an increase in the content of lipid peroxidation products in children with seasonal influenza, regardless of the child's age. It is known that the end products of lipid peroxidation can change the functional activity of phagocytes, inhibit the biosynthesis of superoxide radicals by neutrophils, slow down phagocytosis in monocytes and neutrophils, having pronounced chemotactic activity [24]. The described changes are possible under conditions of a significant deficiency of antioxidant substrates. In our study, we found a pronounced deficiency of fat-soluble vitamins in children with seasonal influenza, regardless of age. At the same time, in young children there was an increase in the oxidized form of glutathione, and at the age of 3–6 years – a decrease in the total antioxidant activity of blood serum. Fat-soluble vitamins (tocopherols and retinol) are present in the fat layer of cell membranes and are able to neutralize free radicals [19]. Alpha tocopherol is the biologically most active of the tocopherols; it limits free radical reactions, being a donor of hydrogen ions, like ascorbate. Due to its lipophilicity, the tocopherol molecule has the ability to integrate into the lipid layer of cell membranes, providing membrane protective and membrane stabilizing effects. Alpha-tocopherol can maintain the functional integrity of the outer plasma membrane of cells, can participate in the mechanisms of tissue respiration in mitochondria, regulate the functioning of cell enzyme systems, thereby preventing LPO activity [24]. The greatest antioxidant properties among retinol precursors has beta-carotene; it has conjugated double bonds and is capable of rapid oxidation using free radical oxidation mechanisms [25]. When antioxidant defense is suppressed, free radical damage occurs to various cell structures and tissues [26, 27].

The results of our study are confirmed by literature data. It is known that in uncomplicated forms of influenza A among pediatric patients, there is a decrease in AOD and a significant increase in LPO processes, depending on the severity of the clinical course of the viral infection. In patients with influenza A who had complications in the form of viral-bacterial pneumonia, AOD is signifi-

cantly weakened, and LPO processes are very active [26]. It was previously studied that influenza produces reactive oxygen species of mitochondrial origin, which destroys lung epithelial cells, leading to their histopathological damage. Pore-forming toxins produced as a result of necroptosis further aggravate the damage to lung tissues and structures, while creating a breeding ground for the spread of pathogenic bacteria [27]. The use of drugs with antioxidant properties in the treatment of viral infections, in particular influenza in children, can lead to the elimination of necroptosis and reduce the severity of the disease complicated by a secondary bacterial infection [27, 28].

Thus, the study confirms the importance of lipid peroxidation processes in the pathogenesis of infectious pathology, including the formation of complicated and uncomplicated forms of seasonal influenza in children.

CONCLUSION

In conclusion, we would like to note that there are higher rates of primary, secondary and end products of lipid peroxidation, and a pronounced lack of fat-soluble vitamins in children with seasonal influenza, regardless of age. In young children, higher levels of the oxidized form of glutathione were observed, in 3–6 years old children – reduced production of antioxidant factors. In connection with the changes in the LPO-AOD system identified in our study, we recommend implementing measures aimed at correcting the above indicators, namely, prescribing medications with antioxidant properties for the treatment of children with seasonal influenza.

Conflict of interests

The authors declare that they have no competing interests.

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Information about the authors

Ekaterina D. Kazantseva – Postgraduate, Junior Research Officer at the Laboratory of Infectology and Immunoprophylaxis, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: kat.smile7@yandex.ru, https://orcid.org/0000-0003-0692-2295

Marina A. Darenskaya – Dr. Sc. (Biol.), Professor of the RAS, Head of the Laboratory of Pathophysiology, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: marina_darenskaya@inbox.ru, https://orcid.org/0000-0003-3255-2013

Lyubov V. Rychkova – Dr. Sc. (Med.), Professor, Corresponding Member of the RAS, Director, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: iphr@sbamsr.irk.ru, https://orcid.org/0000-0002-0117-2563

Alla G. Petrova – Dr. Sc. (Med.), Professor, Head of the Laboratory of Infectology and Immunoprophylaxis, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: rudial75@gmail.com, https://orcid.org/0000-0002-7965-8061

Natalya V. Semenova – Dr. Sc. (Biol.), Deputy Director for Science, Chief Research Officer at the Laboratory of Pathophysiology, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: natkor_84@mail.ru, https://orcid.org/0000-0002-6512-1335

Nadezhda A. Kurashova – Dr. Sc. (Biol.), Academic Secretary, Leading Research Officer at the Laboratory of Pathophysiology, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: nakurashova@yandex.ru, https://orcid.org/0000-0001-8591-8619

Lyudmila A. Grebenkina – Dr. Sc. (Biol.), Leading Research Officer at the Laboratory of Pathophysiology, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: greblud@mail.ru, https://orcid.org/0000-0002-1263-5527

Lyubov I. Kolesnikova – Dr. Sc. (Med.), Professor, Member of the RAS, Honored Scientist of the Russian Federation, Academic Advisor, Scientific Centre for Family Health and Human Reproduction Problems, e-mail: iphr@sbamsr.irk.ru, https://orcid.org/0000-0003-3354-2992

Сведения об авторах

Казанцева Екатерина Дмитриевна – аспирант, младший научный сотрудник лаборатории инфектологии и иммунопрофилактики, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: kat.smile7@yandex.ru, https://orcid.org/0000-0003-0692-2295

Даренская Марина Александровна – доктор биологических наук, профессор РАН, главный научный сотрудник, заведующая лабораторией патофизиологии, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: marina_darenkova@inbox.ru, https://orcid.org/0000-0003-3255-2013

Рычкова Любовь Владимировна – доктор медицинских наук, профессор, член-корреспондент РАН, директор, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: iphr@sbamsr.irk.ru, https://orcid.org/0000-0002-0117-2563

Петрова Алла Германовна – доктор медицинских наук, профессор, заведующая лабораторией инфектологии и иммунопрофилактики, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: rudial75@gmail.com, https://orcid.org/0000-0002-7965-8061

Семенова Наталья Викторовна – доктор биологических наук, заместитель директора по научной работе, главный научный сотрудник лаборатории патофизиологии, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: natkor_84@mail.ru, https://orcid.org/0000-0002-6512-1335

Курашова Надежда Александровна – доктор биологических наук, учёный секретарь, ведущий научный сотрудник лаборатории патофизиологии, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: nakurashova@yandex.ru, https://orcid.org/0000-0001-8591-8619

Гребенкина Людмила Анатольевна – доктор биологических наук, ведущий научный сотрудник лаборатории патофизиологии, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: greblud@mail.ru, https://orcid.org/0000-0002-1263-5527

Колесникова Любовь Ильинична – доктор медицинских наук, профессор, академик РАН, Заслуженный деятель науки РФ, научный руководитель, ФГБНУ «Научный центр проблем здоровья семьи и репродукции человека», e-mail: iphr@sbamsr.irk.ru, https://orcid.org/0000-0003-3354-2992