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CONTENTS

ORIGINAL ARTICLES

- Kateryna M. Borovyk, Olga I. Kadykova, Nataliya G. Ryndina, Volodymyr D. Babadzhan, Oleksandra S. Yermak
 NESFATIN-1 ACTIVITY IN THE BLOOD SERUM IN PATIENTS WITH CHRONIC HEART FAILURE OF ISCHEMIC ORIGIN AGAINST
 THE BACKGROUND OF TYPE 2 DIABETES MELLITUS AND OBESITY 1141
- Tatiana V. Chernii, Volodymyr I. Chemiy, Daria O. Fokina
 MODIFIED ASSESSMENT OF NEUROLOGICAL AND NEUROPSYCHOLOGICAL DEFICIT IN PATIENTS WITH CHRONIC CEREBRAL
 ISCHEMIA AND COMORBIDITY 1146
- Mykhailo D. Diachuk, Tetiana S. Gruzieva, Hanna V. Inshakova
 THE MORBIDITY RATE OF GENITOURINARY DISEASES ACCORDING TO THE DATA ON POPULATION RECEIVING MEDICAL CARE
 IN A MULTIFUNCTIONAL HEALTH CARE FACILITY 1153
- Bogdan S. Fedak, Volodymyr I. Ponomaryov, Valeria V. Ponomaryova, Iryna M. Kravchenko, Olga G. Morozova, Oleksandr A. Yaroshevskiy,
 Oleksandr M. Mishchenko
 DETERMINATION OF SOMATIC, NEUROLOGICAL AND PSYCHO-EMOTIONAL MANIFESTATIONS OF THE ACUTE
 AND POSTCOVID PERIOD IN PATIENTS WITH A MILD COURSE OF COVID-19 IN WARTIME 1160
- Andrii M. Formanchuk, Volodymyr O. Shaprynskyi, Sergiy P. Dmytryshin, Yuriy P. Hnatiyk, Olexandr V. Moskaliuk, Tetiana O. Vozniuk,
 Tetiana V. Formanchuk
 TREATMENT OF COMBAT GUNSHOT SHRAPNEL TRAUMA OF LARGE DEFECTS OF THE SOFT TISSUES OF THE LOWER EXTREMITIES
 WITH PLASTIC SURGERY IN COMBINATION WITH VACUUM ASSISTED WOUND CLOSURE (VAC) 1167
- Tetiana M. Komarova, Oksana P. Vitovska, Yulia I. Komisarenko, Sibylle K. Scholtz
 VITAMIN D LEVEL AND ITS LINK WITH VISUAL ACUITY AND CONTRAST SENSITIVITY IN PATIENTS WITH AGE-RELATED
 MACULAR DEGENERATION 1173
- Vadym A. Kondratiuk, Ivan A. Mazanovych, Nataliya R. Prysyazhna, Andrii V. Ratushniuk, Oleksandr V. Likunov, Yurii M. Hupalo
 ENDOVASCULAR DIAGNOSTICS AND TREATMENT OF HEMORRHAGES IN MILITARY AND CIVILIAN PATIENTS FOLLOWING
 ABDOMINAL SURGERY 1179
- Mykola V. Kvasnitskyi
 MANIFESTATIONS AND TREATMENT OF LOWER BACK PAIN SYNDROME IN WARTIME 1185
- Igor A. Lurin, Igor P. Khomenko, Volodymyr V. Nehoduiko, Serhii V. Tertyshnyi, Vitaly V. Makarov, Ievgen Y. Kvasnevskiy,
 Oleksandr A. Kvasnevskiy
 PROSPECTS OF THE HIGH-SPEED MULTIMEDIA DATA TRANSMISSION TECHNOLOGIES USE IN THE STRUCTURE OF THE SYSTEM
 FOR PROVIDING AID TO INJURED PERSONS HAVING A GUNSHOT DEFECT OF SOFT TISSUES 1191
- Igor A. Lurin, Vitaly V. Makarov, Volodymyr V. Nehoduiko, Kostiantyn M. Smolianyuk, Stepan M. Chobey, Oleksandr Yu. Ott
 GUNSHOT SHRAPNEL WOUND OF THE THIGH WITH DAMAGE TO THE SUPERFICIAL FEMORAL ARTERY (FEATURES OF CLINICAL
 MANIFESTATIONS, DEVELOPMENT OF COMPLICATIONS WITH LATE MEDICAL CARE AND PRESERVATION OF THE LIMB) 1199

Vasyl Z. Netiazhenko, Serhii I. Mostovyi, Olga M. Safonova, Vitaly G. Gurianov, Kyrylo O. Mikhaliiev INTRACARDIAC HEMODYNAMICS, CEREBRAL BLOOD FLOW AND MICROEMBOLIC SIGNAL BURDEN IN STABLE CORONARY ARTERY DISEASE PATIENTS WITH CONCOMITANT COVID-19	1205
Oleksandr L. Nikishyn, Igor V. Altman, Iyad I. Al-Qashkish, Anatoliy I. Gavretskiy, Sergiy I. Savolyuk, Mykola I. Muz DRUG-ELUTING STENTS IN THE TREATMENT OF PATIENTS WITH OCCLUSIVE-STENOTIC LESIONS OF THE SUPERFICIAL FEMORAL ARTER	1216
Alina O. Pletenetska, Ivan S. Demchenko ANALYSIS OF DEFECTS IN THE DIAGNOSIS OF TRAUMATIC BRAIN INJURY FOR THE DECEASED WITHIN 24 HOURS FOLLOWING ADMISSION	1220
Olena V. Ponomarenko, Victor V. Pysanko, Dmytro S. Mialkovskiy, Dmytro V. Tkachuk THE MANAGEMENT OF THE VICTIMS WITH GUNSHOT WOUNDS OF THE EXTREMITIES WITH EXTENSIVE DEFECTS OF THE SOFT TISSUES AT THE LEVEL OF QUALIFIED MEDICAL CARE. CASE-SERIES	1227
Volodymyr O. Shaprynskyi, Vasyl V. Shaprynskyi, Nataliia V. Semenenko MANAGEMENT OF MINIINVASIVE TREATMENT OF PRIMARY VARICOSE SUPERFICIAL VEINS	1233
Vasyl V. Shaprynskyi LATE RESULTS OF TREATING PATIENTS WITH OCCLUSIVE-STENOTIC LESIONS OF THE AORTA INFRARENAL SEGMENT'S MAIN ARTERIES	1239
Olga V. Sherbul, Ilona A. Srebniak, Ivan O. Kuzmuk FLUCTUATING HEARING LOSS AS A SYMPTOM OF ACQUIRED PERILYMPHATIC FISTULA (PLF) UNDER EXTERNAL INJURIES FACTOR	1246
Volodymyr O. Shkorbotun, Olena O. Dyadyk, Yaroslav S. Nachesa MORPHOLOGICAL FEATURES OF MAXILLARY SINUS CYSTS BASED ON THE STUDY OF PARTICULAR HISTOCHEMICAL AND IMMUNOHISTOCHEMICAL FACTORS OF INFLAMMATION	1252
Ivan M. Todurov, Oleksandr V. Perekhrestenko, Sergii V. Kosiukhno, Viktoriia V. Yevsieieva, Yurii B. Lisun ASSESSMENT OF THE EFFICIENCY OF ANALGETIC ACTION OF LAPAROSCOPICALLY ASSISTED TAP BLOCK AS A COMPONENT OF PERIOPERATIVE MULTIMODAL ANALGESIA PLAN IN OBESE PATIENTS UNDERGOING METABOLIC SURGERY	1259
Volodymyr M. Tverezovskiy, Valeriy A. Kapustnyk, Borys O. Shelest, Nataliia K. Sukhonos ASSOCIATION OF CASPASE-8 LEVELS WITH RESPIRATORY PARAMETERS AND PRESENCE OF HYPERTENSION IN COPD PATIENTS	1265
Lyudmila A. Ustinova, Borys I. Palamar, Yevhen V. Havrylko, Vitaliy L. Bohaienko, Natalia V. Kurdil ASSESSMENT OF THE CONSEQUENCES OF THE DETERIORATION OF THE EPIDEMIOLOGICAL SITUATION DURING HOSTILITIES	1272
Tetiana V. Vasheka, Oksana M. Lych, Borys I. Palamar, Svitlana P. Palamar, Victoria V. Zhelanova, Tetiana Yu. Safir, Natalia V. Kurdil PSYCHOLOGICAL FACTORS OF STUDENTS'VITALITY DURING THE WAR IN UKRAINE	1279

Yuliya V. Volkova, Halyna V. Tsymbaliuk, Valeria V. Ponomaryova, Dmytro V. Dmytriiev, Kostiantyn D. Dmytriiev, Viktoriia I. Iievleva, Inna S. Borodai DYNAMICS OF INDICATORS IN PLATELET HEMOSTASIS IN POLYTRAUMA AND ENLARGED BODY MASS INDEX	1285
Vira V. Zlatkina, Valeriya D. Nemtsova, Bogdan S. Fedak, Volodymyr I. Ponomaryov, Natalia M. Zhelezniakova, Oleksandr M. Mishchenko, Dariia V. Horban FUNCTIONAL CHARACTERISTICS OF THE CARDIOVASCULAR SYSTEM OF PATIENTS WITH ISCHEMIC HEART DISEASE WITH OBESITY	1290
Oleksandr Yu. Ioffe, Oleksandr P. Stetsenko, Stepan L. Kindzer, Mykola S. Kryvopustov, Yuri P. Tsiura, Yevhenii S. Prykhodko APPLICATION OF PROBIOTIC ANTISEPSIS FOR PURULENT COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS	1295
Valentina M. Sokolovska, Natalia V. Tsvetkova, Oleg A. Pisarenko, Viktor V. Kuznetsov, Iryna A. Holovanova, Natalia A. Lyakhova WAYS OF IMPROVING THE QUALITY OF PROSTHETICS OF MILITARY PERSONNEL	1302
Yulia G. Kolenko, Tetiana O. Timokhina, Olesya V. Lynovytska, Olena V. Cherkasova, Konstantin E. Pechkovskyi CLINICAL AND IMMUNOLOGICAL FEATURES OF THE COURSE OF CARIES IN YOUNG PEOPLE WHO HAVE SUFFERED A CORONAVIRUS INFECTION	1309

ORIGINAL ARTICLE

CLINICAL AND IMMUNOLOGICAL FEATURES OF THE COURSE OF CARIES IN YOUNG PEOPLE WHO HAVE SUFFERED A CORONAVIRUS INFECTION

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ABSTRACT

The aim: To establish the clinical and immunological features of the course of caries in young people who have suffered from the coronavirus disease.

Materials and methods: The main group consisted of 30 people aged $20,6 \pm 2,4$ years who suffered from the Covid19 coronavirus infection $6,1 \pm 1,2$ months ago. All patients underwent a dental and immunological examination.

Results: The analysis of the indicators of the dental status revealed the possibility of the existence of a relationship between the signs of the transferred acute viral infection SARS-CoV2 and the development of dental caries, first, under the condition of reduced caries resistance. In the immune system of the examined patients were found significant changes, which definitely played a pathogenetic role in the development and progression of the carious process. They were manifested by changes of varying degrees of severity, which were both unidirectional and opposite in nature: T-lymphocyte deficiency, in particular, mainly due to T-cytotoxic lymphocytes/suppressors, an increased level of B-lymphocytes and an increased level of activated CD54+ cells of T-lymphocytes.

Conclusions: In young people with dental caries who have suffered a coronavirus infection during the last 6 months, the prevalence of caries and its intensity are significantly higher than in the comparison group. Violations in the cellular and humoral links of the immune system, which combined with the pro-inflammatory profile of the blood serum, the phenomenon of immunotoxicosis, contributed to the further progression of the carious process in the oral cavity.

KEY WORDS: caries, coronavirus disease, young age, immunological parameters, cytokines, circulating immune complexes

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INTRODUCTION

A large-scale problem in the world is the SARS-CoV-2 coronavirus, which causes coronavirus disease (COVID-19), characterized by a large number of complications - "post-COVID syndrome" [1-5]. Analysis of the protective value of humoral immunity and the duration of its intensity is important for scientists because of the need to indicate the level of antibodies to SARS-CoV-2 for laboratory diagnosis and prevention of the recurrence of coronavirus disease [3, 6, 7]. One of the pathogenetic strategies of the virus is the ability to provoke the aggression of the immune system against its own tissues in the form of autoimmune and autoinflammatory processes, which is considered a unique feature of the survival of β -CoV in the body of an infected person [4].

Zinchuk O.M. and co-author Velavan T.P. and the co-author note that «activity of the synthesis of anti-coronavirus antibodies is directly proportional to the intensity of the infectious process. Therefore, in severe cases of the disease, antibody production indicated at

the highest level and antibodies detected in the blood serum longer, while in mild cases and with an asymptomatic course of the infectious process, antibodies to SARS-CoV-2 often have a minimal level or not defined at all» [6, 8]. Also, Velavan T.P. and the co-author note that «level of anti-coronavirus antibodies usually decreases within a few months after infection, and the neutralizing activity of antibodies after symptomatic cases of COVID-19 in most patients persists for 6-8 months. In addition to disease severity, the duration of humoral immunity is likely to depend on baseline antibody levels» [8]. Data from the US Centers for Disease Control and Prevention (CDC) shows that there is a high probability of the simultaneous presence of IgM and IgG in patients who has just been infected with the coronavirus. This is a feature of COVID-19 [1,2]. In addition to various examination methods, laboratory indicators also help in assessing the degree of severity, diagnosing complications, and predicting the course of the disease [9, 10].

It is well known that dental caries is a multifactorial

disease, the elimination of this disease is the main task of dentistry [11-13]. The non-specific resistance of the organism has an indirect effect on mineralization processes [12]. There are many oral symptoms in COVID-19 [14-16], but the coexistence with the underlying disease is not fully established. It is still not clear whether oral symptoms are manifestations of the disease or arise from a loss of immune response [14,17].

There is evidence that immune functioning associated with periodontitis and (less studied) dental caries changes with age. In both cases, age-related mechanistic changes in the functioning of the immune system are complex and not fully studied, and it is not clear how they correlate with disease susceptibility [18]. Study have shown that caries affects the inflammatory and oxidative status of the periodontium, while its treatment appears to restore periodontal homeostasis [19]. Also needed studies with longer follow-up in order to assess the impact of the pandemic on dental caries [20].

THE AIM

To determine the clinical and immunological features of the course of caries in young people who have suffered from coronavirus disease.

MATERIALS AND METHODS

The main group consisted of 30 people who had Covid19 infection, mostly of mild and moderate severity, and had caries. The comparison group consisted of 20 people who had caries but did not have coronavirus infection. The control group consisted of 35 people, randomized by age and gender, who did not have signs of caries and did not have a coronavirus disease. The mean age of the examined patients was $20,6 \pm 2,4$ years. In the main group of patients, the duration from the moment when there was a disease with coronavirus disease to the moment of inclusion in the study was $6,1 \pm 1,2$ months.

The patients selected for this study underwent a dental examination. Determination of the prevalence and intensity of dental caries, the state of oral hygiene and periodontal tissues was determined using the following indexes: Average of Decayed, Missing, and Filled Teeth index (DMFT); Standard Deviation of Decayed, Missing, and Filled Teeth index (SD of DMFT); Average of Oral Hygiene Index Score (OHIS) (OHI-S); Interdental Hygiene Index (IDHI) and Gingival Index (GI), Löe and Silness.

The immunological status studied of the studied cohort of patients, namely: quantitative assessment of the main populations and subpopulations of lymphocytes, determination of their functional activity, concentration

of circulating immune complexes of various molecular sizes, serum immunoglobulin levels, phagocytic activity of neutrophils, and cytokine status by level I and II tests according to requirements WHO Memorandum [21].

The following were evaluated: phenotype of lymphoid cells, lymphocyte subpopulations – CD3+ lymphocytes (T cells); CD4+ lymphocytes (T-helpers); CD8+ lymphocytes (T-cytotoxic lymphocytes/suppressors); CD16+ lymphocytes (NK cells), CD22+ lymphocytes (B cells), CD54+ lymphocytes (activated lymphocytes that express the adhesion molecule ICAM-1), CD95+ lymphocytes (activated lymphocytes that express the FAS receptor) - by indirect immunofluorescence method using monoclonal antibodies manufactured by CJSC "Sorbert-Service" against lymphocyte antigens CD 3, CD 4, CD 8, CD 16, CD 22, CD 54, CD 95 with a final count of 200 cells of each phenotype on a «Lumam I3» fluorescent microscope; the functional activity of T-lymphocytes by the morphological method of the proliferative activity of lymphocytes in the reaction of blast transformation of lymphocytes (RBTL) with the mitogen phytohemagglutinin (PHA-M) of the "Wellcome Burroughs" company; phagocytic activity of neutrophils according to the degree of absorption of latex particles with the calculation of Hamburg's phagocytic index and Wright's phagocytic number; the functional state of B-lymphocytes by examining the level of the main classes of serum immunoglobulins Ig G, Ig A, Ig M by the method of simple radial immunodiffusion in a gel according to G. Mancini et al., 1965; the concentration of circulating immune complexes (CIC) in blood serum - by the method of precipitation in a solution of polyethylene glycol (PEG-6000) on a microspectrophotometer "Specol-21" (Germany) at a wavelength of 450 nm [21].

Descriptive analysis results presented as percentage distribution, mean and standard deviation (SD), or median and interquartile range (IQR). Chi-square and Fisher's exact test is used to determine any differences in the distribution of categorical variables. Because continuous variables did not follow a normal distribution, Kruskal-Wallis analysis of variance and Mann-Whitney U-test is used to detect differences in means between two or three groups. All exposure variables were included in a multivariable regression model. Results of regression analysis presented as unadjusted and adjusted odds ratios (ORs) with their 95% CIs. The level of significance was set at $p < 0.05$. Statistical data processing was also determined by the method of variational statistics using the Microsoft XP "Excel" application program package and the specialized "STATGRAPHICS Plus version 2.1" program.

Table I. Dental status of persons who have suffered from the coronavirus disease

	Main	Control
Average of DMFT	3.2	2.1
SD of DMFT	2.1	1.4
Average of OHI-S	1.44	1.1

The average and standard deviation of DMFT in main group from control group was 3.2 and 2.1, respectively, the average and standard deviation of DMFT was 2.1 and 1.4, for main group from control ($P < 0.01$).

Table II. Index indicators of the dental status of persons with caries who suffered from the coronavirus disease ($M \pm m$)

	Main	Control
IDHI	$1,55 \pm 0,28$	$0,82 \pm 0,43$
GI, Löe ta Silness	$1,81 \pm 0,36$	$0,79 \pm 0,64$

Table III. The content of the main and activated subpopulations of lymphocytes in the examined persons ($M \pm m$)

Immunological indicators	Main group (n=30)	Comparison group (n=20)	Control group (n=35)
Leukocytes, $\times 10^9/n$	$6,13 \pm 0,41$	$5,70 \pm 1,20$	$7,76 \pm 0,82$
Lymphocytes, %	$43,15 \pm 1,27$	$44,25 \pm 1,14$	$32,14 \pm 3,70$
CD3 ⁺ lymphocytes, %	$53,4 \pm 1,3^*$	$61,6 \pm 1,2x$	$64,31 \pm 4,03$
CD4 ⁺ lymphocytes, %	$33,8 \pm 1,2$	$34,8 \pm 1,7$	$33,23 \pm 3,90$
CD8 ⁺ lymphocytes, %	$14,8 \pm 0,9^*$	$18,6 \pm 0,8x$	$20,50 \pm 2,05$
CD4 ⁺ /CD8 ⁺	$2,92 \pm 0,1^*$	$1,8 \pm 0,1^*x$	$1,61 \pm 0,29$
CD22 ⁺ lymphocytes, %	$32,6 \pm 1,4^*$	$25,2 \pm 1,2x$	$21,06 \pm 1,17$
CD16 ⁺ lymphocytes, %	$12,3 \pm 1,1^*$	$16,8 \pm 1,1x$	$16,7 \pm 1,11$
CD95 ⁺ lymphocytes, %	$11,21 \pm 0,32^*$	$6,77 \pm 0,23x$	$5,04 \pm 0,02$
CD54 ⁺ lymphocytes, %	$21,2 \pm 1,03^*$	$13,4 \pm 1,05x$	$13,8 \pm 0,81$

Notes:

*— the difference between the indicator and the control group is significant ($p < 0.05$);

x - the difference in the indicator between the groups is significant ($p < 0.05$);

n - the number of patients.

Table IV. Indicators of functional activity of immunocompetent cells in the examined persons ($M \pm m$)

Immunological indicators	Main group (n=30)	Comparison group (n=20)	Control group (n=35)
RBTL spontaneous, %	$2,42 \pm 0,12^*$	$1,98 \pm 0,08x$	$1,77 \pm 0,22$
RBTL from PHA-M, %	$76,41 \pm 2,75$	$79,27 \pm 2,11$	$78,3 \pm 3,97$
Phagocytic number	$3,47 \pm 0,12^*$	$3,48 \pm 0,09^*$	$5,97 \pm 0,34$
Phagocytic index, %	$49,73 \pm 2,13^*$	$48,44 \pm 3,05^*$	$67,53 \pm 4,41$
NBT-test, spontaneous, %	$36,12 \pm 2,21^*$	$38,03 \pm 1,95^*$	$24,69 \pm 1,89$

Notes:

*— the difference between the indicator and the control group is significant ($p < 0.05$);

x - the difference in the indicator between the groups is significant ($p < 0.05$);

n - the number of patients.

RESULTS

DENTAL STATUS OF THE EXAMINED PATIENTS

The assessment of the dental status of the examined young persons with dental caries who suffered coronavirus disease is given in Tables I and II.

The average and standard deviation of DMFT in main group from control group was 3.2 and 2.1, respectively, the average and standard deviation of DMFT was 2.1 and 1.4, for main group from control ($P < 0.01$).

During the examination were primarily diagnosed deep caries of the molars and caries in the area of the tooth neck. Complaints were mainly about short-term,

Table V. Serum concentration of the main classes of immunoglobulins and CIC in the examined persons (M±m)

Immunological indicators	Main group (n=30)	Comparison group (n=20)	Control group (n=35)
Ig G, g/l	17,31±1,03*	12,45 ± 0,98 x	12,73±1,25
Ig A, g/l	2,56 ± 0,16*	1,32±0,17 x	1,59±0,11
Ig M, g/l	0,99 ± 0,02	80,93±0,11	1,01±0,07
CIC of large size (>19S), c.u.	33,08 ± 2,21*	47,24±2,13x	52,5±4,02
CIC of medium size (11-19S) c.u.	42,26 ± 2,16*	34,11±1,96 x	30,96±3,52
CIC of small size (<11 S), c.u.	32,22 ± 1,82*	20,16±2,31*x	15,23±1,07

Notes:

*— the difference between the indicator and the control group is significant (p<0.05);

x - the difference in the indicator between the groups is significant (p<0.05);

n - the number of patients.

Table VI. Concentration of pro- and anti-inflammatory cytokines in blood serum of examined patients (M±m)

Immunological indicators	Main group (n=30)	Comparison group (n=20)	Control group (n=35)
TNF-α, пг/мл	82,6 ± 3,1*	64,9±2,4*x	51,3±4,1
IL-1β, пг/мл	82,6±2,4 *	57,2±3,6 *x	46,9±2,98
IL-6, пг/мл	12,3±0,9	11,4±0,7	12,94±1,2
IL-4, пг/мл	19,1±1,3 *	23,5±1,2 x	22,41±1,4

Notes:

*— the difference between the indicator and the control group is significant (p<0.05);

x - the difference in the indicator between the groups is significant (p<0.05);

n - the number of patients.

involuntary pain from sweets in the examined teeth. The patients indicated that they had not visited a dentist from the time they had a coronavirus disease to the time of inclusion in the study for 6.1 ± 1.2 months. The main reason is the unavailability of dental clinics during the pandemic. In addition, according to the respondents, they were periodically in a state of stress due to the uncertainty of the future due to the pandemic, fear for the health of their relatives, and perhaps began to consume more sweet carbonated drinks and sweets. As can be seen from the data presented in Table 2, significantly higher values of hygienic indices were found in the patients of the main group, which indicates a much deeper character of periodontal tissue damage and tooth pathology with the formation of dentition defects.

INDICATORS OF SYSTEMIC IMMUNITY IN YOUNG PEOPLE WITH CARIES WHO HAVE SUFFERED A CORONAVIRUS INFECTION

The main indicators of the cellular link of the immune system in the examined young people are presented in the Table. III.

The data shown in Table 3 demonstrate that the total number of leukocytes and the percentage of lymphocytes in the peripheral blood in both groups of examined persons were preserved and corresponded to the normative values.

The results of the study of the cellular link of immunity showed that the level of CD3+ cells in the primary patients was probably lower than the similar indicator in the comparison group by 13.3% (p<0.05), and the content of T-cytotoxic lymphocytes/suppressors (CD8+ lymphocytes) - by 20.4% (p<0.05). In both groups of patients, an imbalance of immunoregulatory subpopulations revealed, while the level of CD4+ lymphocytes corresponded to normative indicators, and the percentage level of CD8+ lymphocytes was significantly lower than the indicator of the control group in the comparison group.

At the same time, a probable increase in the percentage of CD22+ cells in the examined main group was found, which indicates a significant activation of the B-cell link of the immune system in response to the chronic persistence of infectious antigens on the mucous membrane and transferred coronavirus infection. Also, in both groups of patients, was detected a probable increase in the content of activated lymphocytes that express the FAS receptor and ready for apoptosis, however, in patients of the main group, the level of CD95+ lymphocytes was higher than that of the comparison group. This is due to greater activity of inflammatory changes in the oral cavity and probably higher serum concentration of TNF-α, the main cytokine of inflammation. It should be noted that in the main group of examined patients was found a probably high-

er level of CD54+ lymphocytes, which participate in the adhesion process and express the adhesion molecule ICAM-1. Which is a consequence of impaired adhesion and cooperation of immunocompetent cells for a long time after the coronavirus infection.

The study of the functional activity of immunocompetent cells in the examined individuals of the main group (Table IV) showed high indicators of spontaneous proliferative activity of lymphocytes compared to the data of the control group ($p < 0.05$), while the stimulated PHA-M proliferative activity of lymphocytes had no significant differences from normative values.

A significant decrease in phagocytosis indicators observed in the examined persons of both groups. Studies have shown that the index of phagocytic number and phagocytic index in the main group of patients was lower ($p < 0.05$) than the values in healthy individuals and patients of the comparison group.

In the data of patients, it was determined that long-term persistence and antigenic stimulation by various bacteria caused an increase in the metabolic activity of neutrophils.

Table V shows data on the serum concentration of the main classes of immunoglobulins and CIC.

During the study of indicators of humoral immunity in the examined persons, a probable increase in the serum concentration of IgG and IgA was found in the main group of patients ($p < 0.05$).

It should be noted that in the main group of patients there was an imbalance in the level of CICs in the blood serum, which was manifested by an increase in the content of pathogenic medium and small molecular CICs with a significant decrease in physiological CICs of large size, which is associated with the development of subclinical inflammation as a consequence of the transferred coronavirus infection.

Therefore, more pronounced phenomena of immunotoxicosis were observed in the main group of patients, which requires further dynamic monitoring.

The analysis of the data presented in Table VI showed a high activity of pro-inflammatory cytokines in the blood serum of examined caries patients, which was probably higher in persons who had undergone a coronavirus infection. Thus, in patients of the main group, the level of TNF- α and the content of IL-1 β in blood serum exceeded the indicator in the comparison group, with therefore, the level of IL-6 in both groups of patients had no significant differences between them ($p > 0.05$) and corresponded to normative values ($p > 0.05$). TNF- α is a key starting pro-inflammatory cytokine that triggers an inflammatory reaction, participates in disturbances in the cellular link of the immune response, and increases the level of activated lymphocytes. IL-1 β has the same

properties. IL-6 is a cytokine that ends the inflammatory response, but since all subjects taken into the study before treatment, its level remained within the range of healthy individuals. In the main group of patients was found decrease in the level of anti-inflammatory IL-4, which was compensatory in nature.

DISCUSSION

Thus, we conducted a clinical and immunological examination of young people with dental caries who suffered mild and moderate coronavirus infection. 6,1 $\pm$ 1,2 months passed from the moment of contracting the coronavirus disease to the moment of inclusion in the study.

Analysis of indicators of dental status revealed that within 6 months after experiencing the coronavirus disease in the examined patients, its indicators significantly worsened: the prevalence of caries was significantly higher than in the comparison group. The indicator of the intensity of dental caries was also higher than that of patients in the control group. From the above data, it follows that the intensity of dental caries is approximately 2 times higher in patients with a history of coronavirus infection than in the examined persons in the control group ($p < 0.05$). It was shown that the values of the resistance of hard tissues to the effects of caries-causing factors are related to the intensity of dental caries damage. This indicates the existence of a relationship between the signs of an acute SARS-CoV2 viral infection and the development of dental caries, first of all, under the condition of reduced caries resistance.

Similar results were found in Matsuyama Y. et al. (2022): in children previously infected with COVID-19, dental caries was more common than in those who escaped the lesion and slightly increased after the pandemic [20]. Due to the tropism of the virus to mucous membranes, Paradowska-Stolarz (2021) was attempted to describe the oral manifestations of SARS-CoV-2 infection: «Angiotensin-converting enzyme 2 (ACE-2), which ensures the attachment of the virus, is also present in the oral cavity.» The analysis of the scientific study showed that the most common oral symptoms are dysgeusia (disturbance of taste), toothache, exacerbation of autoimmune diseases, as well as infection with herpes simplex and chickenpox viruses. Ulcers and aphthous stomatitis are also often mentioned. The author emphasizes that there are many oral symptoms in COVID-19, but the coexistence with the main disease is not fully established [14]. To assess the impact of the pandemic on dental caries in children, studies with longer follow-up are needed [20]. At the same time, studies assessing the impact of the global

pandemic on the prevalence of caries were almost impossible to find [17].

Significant changes in the immune system were found in the examined patients, which definitely played a pathogenic role in the development and progression of the carious process. They were manifested by changes of varying degrees of severity, which were both unidirectional and opposite in nature: T-lymphocyte deficiency, in particular, mainly due to T-cytotoxic lymphocytes/suppressors, an increased level of B-lymphocytes and an increased level of activated CD54+ cells of T-lymphocytes.

Violations in the cellular and humoral links of the immune system, which were combined with the pro-inflammatory profile of the blood serum, the phenomenon of immunotoxicosis, contributed to the further progression of the carious process in the oral cavity with the formation of a «vicious circle» of the combined pathology.

CONCLUSIONS

1. In young people with dental caries who have suffered a coronavirus infection during the last 6 months, the prevalence of caries and its intensity are significantly higher than in the comparison group, significantly higher values of the bleeding index, PMA index and hygiene index are found, which indicates deeper tissue damage and tooth pathology with the formation of dentition defects.
2. In the immune system of young people with dental caries who suffered from coronavirus infection during the last 6 months, signs of immunodeficiency were detected, primarily a decrease in the level of T-lymphocytes and T-cytotoxic lymphocytes/suppressors, which are accompanied by B-lymphocytosis and manifestations of hyperimmunoglobulinemia and activation pro-inflammatory changes with an increase in serum concentrations of TNF- α and IL- β .

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The Authors declare no conflict of interest.

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