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ИНТЕГРАЛЬНОЕ ИССЛЕДОВАНИЕ АКТИВНОСТИ СИМПАТОАДРЕНАЛОВОЙ СИСТЕМЫ И ОСОБЕННОСТЕЙ ИММУННОГО ОТВЕТА ПРИ ПОСТКОВИДНОМ РЕВМАТОИДНОМ АРТРИТЕ.

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Аннотация. В конце 2020 г. инфекция SARS-CoV-2 (Severe Acute Respiratory coronavirus 2), вызвавшая пандемию коронавирусной болезни 2019г. (coronavirus disease, COVID-19), поразила более 40 млн. человек и привела к более чем 1,2 млн. летальных исходов [1]. COVID-19 явился серьезным вызовом человечеству. В процессе развития пандемии вскрылось большое число новых фундаментальных и медицинских проблем, и многих распространенных хронических неинфекционных заболеваний, среди которых одну из важных позиций занимают ревматические и мышечно-скелетные заболевания (РМСЗ) [3], в спектре которых центральное место занимают иммуновоспалительные ревматические заболевания (ИВРЗ). ИВРЗ, характеризуются прогрессирующей патологией суставов, мышц, костей и внутренних органов, приводя к инвалидности, снижению качества и уменьшению продолжительности жизни. Современная концепция патогенеза COVID-19, в основе которой лежат представления о своеобразной вирус-индуцированной дисрегуляции (асинхронизации) врожденного и приобретенного иммунитета, приводящей к гиперпродукции широкого спектра провоспалительных, антивоспалительных и иммунорегуляторных цитокинов и других медиаторов воспаления [6,7,8].

Ключевые слова: Цитокины, ревматоидный артрит, COVID-19, аутоиммуные заболевания,симпатоадреналовая система.

AN INTEGRATED STUDY OF THE ACTIVITY OF THE SYMPATHO-ADRENAL SYSTEM AND THE CHARACTERISTICS OF THE IMMUNE RESPONSE IN POST-COVID RHEUMATOID ARTHRITIS.

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Annotation. At the end of 2020, SARS-CoV-2 (Severe Acute Respiratory coronavirus 2) infection, which caused the 2019 coronavirus disease (COVID-19) pandemic, affected more than 40 million people and led to more than 1.2 million deaths [1]. COVID-19 has posed a serious challenge to humanity. In the course of the development of the pandemic, a large number of new fundamental and medical problems have been revealed, and many common chronic non-communicable diseases, among which rheumatic and musculoskeletal diseases (RMSD) occupy one of the important positions [3], in the spectrum of which immunoinflammatory rheumatic diseases (RWRI) occupy a central place. MVRI are characterized by progressive pathology of joints, muscles, bones and internal organs, leading to disability, reduced quality of life and reduced life expectancy. The modern concept of the pathogenesis of COVID-19, which is based on the of a kind of virus-induced dysregulation (asynchronization) of innate and acquired immunity, leading to hyperproduction of a wide range of pro-inflammatory, anti-inflammatory, and immunoregulatory cytokines and other inflammatory mediators [6,7,8].

Key words: Cytokines, rheumatoid arthritis, COVID-19, autoimmune diseases, sympathoadrenal system.

КОВИДДАН КЕЙИНГИ РЕВМАТОИД АРТРИТДА СИМПАТО-АДРЕНАЛ ТИЗИМИ ФАОЛЛИГИ ВА ИММУН ЖАВОБ ХУСУСИЯТЛАРИНИ КОМПЛЕКС ЎРГАНИШ.

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Annotatsiya. 2020 yil oxirida koronavirus kasalligi 2019 pandemiyasiga (koronavirus kasalligi, COVID-19) sabab bo'lgan SARS-CoV-2 (Og'ir o'tkir respiratorli koronavirus 2) infektsiyasi 40 milliondan ortiq odamga ta'sir qildi va 1,2 milliondan ortiq o'limga olib keldi [1]. COVID-19 insoniyat uchun jiddiy muammoga aylandi. Pandemiyaning rivojlanishi ko'plab yangi fundamental va tibbiy muammolar va ko'plab keng tarqalgan surunkali yuqumli bo'lmagan kasalliklarni aniqladi, ular orasida revmatik va tayanch-harakat tizimi kasalliklari (RMSD) muhim o'rinni egallaydi [3], ularning spektrida immun yallig'lanishli revmatik kasalliklar (IIRD) markaziy o'rinni egallaydi. IRD bo'g'imlarning, mushaklarning, suyaklarning va ichki organlarning progressiv patologiyasi bilan tavsiflanadi, bu nogironlikka, hayot sifatining pasayishiga va umr ko'rish davomiyligining pasayishiga olib keladi. Yallig'lanishga qarshi, yallig'lanishga qarshi va immunoregulyatsion sitokinlar va boshqa yallig'lanish vositalarining keng assortimentida giperproduksiyaga olib keladigan tug'ma va orttirilgan immunitetning virus tomonidan qo'zg'atilgan disregulyatsiyasi (asinxronizatsiyasi) g'oyasiga asoslangan COVID-19 patogenezining zamonaviy kontseptsiyasi [6,7,8].

Kalit so'zlar: sitokinlar, revmatoid artrit, COVID-19, autoimmun kasalliklar, simpatoadrenal tizim.

Aim. Study of the activity of the sympathetic-adrenal system and the state of immunological status in patients with post-COVID rheumatoid arthritis

Materials and methods of research. To assess the features of CAC activity disorders in RA patients, the levels of catecholamines in urine, vanillyl-mandelic acid in urine, and monoamine oxidase in serum in patients were determined. As a result of the research, it was found that neurohumoral factors, in particular, A and HA occupy a special place in the cohort of clinical and laboratory studies of patients with autoimmune diseases. 55 patients with rheumatoid arthritis and patients who had COVID19 infection aged 20-75 years, who underwent inpatient examination and treatment in the therapeutic departments of the AGMI Clinics from 2021-2023. All participants were randomized into four groups depending on the clinical manifestations of post-COVID syndrome. Each group included a comparable number of patients, taking into account gender, age, duration of the underlying disease and the form of the course of coronavirus infection. Group I: control, consisted of 18 examined at the age of 28 to 63 years, practically healthy people, whose average age was 38.9±2.5 years. Group II: consisted of 20 patients with RA of unknown etiology, with an average age of 47.8±0.7 years. Group III: consisted of 17 patients who had COVID-19 infection with subsequent development of RA, whose average age was 32.9±2.3 years. Group IV: 18 RA patients exposed to COVID-19 infection, with an average age of 42.9±1.7 years.

Results of the study. The study of daily excretion of A in the examined patients with autoimmune nature showed a statistically significant increase in A: free A – 5.9±0.47 μg/day, conjugated A – 5.31±0.39 μg/day, total A – 11.21±0.49 μg/day; which is 37.5% (1.4-fold), 36.2% (1.4-fold), 36.9% (1.4-fold) (P<0.001) higher than the control indicators, respectively. In patients with RA-19 etiology, the largest persistent increase in the level of A was noted, which amounted to free A – 7.1±0.8 μg/day, conjugated A – 6.94±0.7 μg/day, total A – 14.04±0.46 μg/day; which, respectively, is 65.5% (1.7-fold), 77.9% (1.8-fold), 71.4% (1.7-fold) (P<0.001) higher than the control indicators. RA patients infected with COVID-19 showed an increase in the A level, but less pronounced in relation to RA-19 patients of COVID-19 etiology, which amounted to free A – 6.7±0.4 μg/day, conjugated A – 6.1±0.37 μg/day, total A – 12.8±0.61 μg/day; which is respectively 56.2% (1.6-fold), 56.4% (1.6-fold), 56.3% (1.6-fold) (P<0.001) higher than the control indicators (Table 1).

Daily excretion of free, conjugated, total A in patients with autoimmunity.

Table 1.

RA, RA COVID-19 etiology, RA+ COVID-19 (M±m, μg/day) Groups of surveyed	Adrenaline		
	free.	conjug.	Amounts.
Control Group (n=18)	4,29±0,33	3,9±0,35	8,19±0,326
G. RA of autoimmune nature (n=20)	5,9±0,47	5,31±0,39	11,21±0,49
G. RA COVID-19 etiology (n=17)	7,1±0,8	6,94±0,7	14,04±0,46
G. RA+ COVID-19 (n=18)	6,7±0,4	6,1±0,37	12,8±0,61
P_{1-2}	<0,01	<0,01	<0,01
P_{1-3}	<0,001	<0,001	<0,001
P_{1-4}	<0,05	<0,05	<0,05
P_{2-3}	<0,05	<0,05	<0,05
P_{2-4}	<0,05	<0,05	<0,05
P_{3-4}	<0,05	<0,05	<0,05

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With regard to HA, patients with RA of autoimmune nature also showed a statistically significant increase (Table 3), which amounted to: free HA - up to 10.7±0.5 μg/day, conjugated HA - up to 9.4±0.43 μg/day, total HA - up to 20.1±0.63 μg/day; which is 32.1% (1.3-fold), 31.5% (1.3-fold), 31.8% (1.3-fold) (P<0.001) higher than the control level values, respectively. RA patients examinedCOVID-19 etiologies showed a statistically significant increase, which amounted to: free HA - up to 12.1±0.6 μg/day, conjugated HA - up to 10.3±0.49 μg/day, total HA - up to 22.4±0.74 μg/day; which, respectively, is 49.4% (1.5-fold), 44.1% (1.4-fold), 46.9% (1.5-fold) (P<0.001) higher than the indicators of the control group, and in addition, gave the highest values. In the group of patients RA infected with COVID-19 also showed an increase in the level of HA, which was less pronounced in relation to patients with RA COVID-19 etiology. The indicators were free HA – 11.7±0.52 μg/day, conjugated HA – 10.2±0.48 μg/day, total A – 21.9±0.65 μg/day; which is 44.4% (1.4 times), 42.7% (1.4 times), 43.6% (1.4 times) (P<0.001) higher than the control indicators, respectively. Depending on gender, the highest A index was determined in females of the group of patients with RA COVID-19 etiology, which amounted to 14.39±0.7 μg/day, which is 30.7% (1.3 times) more than the group of patients with RA of an autoimmune nature, 29.8% more than the group of patients with RA + COVID-19. As for UA, the same pattern was observed. In patients with RA COVID-19 etiology of females, the indicators of HA were the highest, which is 11.4% (1.1 times) higher than the indicators of patients with RA of autoimmune nature and by 5.9% (1.06 times) more than the rates of patients with RA + COVID-19.

Table 2. Daily excretion of free, conjugated, total HA in patients with autoimmunity

R A, RA COVID-19 etiology, RA+ COVID-19 (M±m, μg/day) Группы обследованных	Norepinephrine		
	free.	conjug.	Amounts.
Control Group (n=18)	8,1±0,31	7,15±0,36	15,25±0,5
G. RA of autoimmune nature (n=20)	10,7±0,5	9,4±0,43	20,1±0,63
G. RA COVID-19 etiology (n=17)	12,1±0,6	10,3±0,49	22,4±0,74
G. RA+ COVID-19 (n=18)	11,7±0,52	10,2±0,48	21,9±0,65
P_{1-2}	<0,01	<0,01	<0,01
P_{1-3}	<0,001	<0,001	<0,001
P_{1-4}	<0,05	<0,05	<0,05
P_{2-3}	<0,05	<0,05	<0,05
P_{2-4}	<0,05	<0,05	<0,05
P_{3-4}	<0,05	<0,05	<0,05

Taking into account the data on males, it can be noted that the levels of A and HA, respectively, are more often increased in women: A 14.39±0.7 μg/day versus 13.7±0.7 μg/day (p>0.05) and 23.4±0.72 μg/day versus 21.7±0.63 μg/day (p>0.05). Thus, in most cases, patients with RA have all the signs of metabolic disorders A and NA, which ensures the development of effective methods for the diagnosis and subsequent therapy of this category of patients. We also compared the levels of catecholamines depending on age. It was found that in RA patients, the concentration of CA reached higher values in young age groups. A more pronounced trend is observed in the group of

patients with RA COVID-19 etiology: the level of total A was 16.7±0.82 μg/day in the age group of 30-39 years, the level of total HA was 26.7±0.87 μg/day. Thus, it can be said that there is an age-related exhaustion of the activity of many body systems, and in particular CAC.

With regard to DA, a statistically insignificant increase in the daily excretion of all DA fractions was observed in the group of patients with autoimmune nature, which amounted to: free DA – 191.2±9.4 μg/day, conjugated DA – 188.5±7.6 μg/day, total DA – 379.7±13.9 μg/day; which is 7.4% (1.1-fold), 2.4% (1.02-fold), 4.9% (1.05-fold) ($P<0.05$) higher than the control indicators, respectively. The indicators of the comparative groups of RA-19 patients of etiology were as follows: free DA – 201.7±9.6 μg/day, conjugated DA – 198.5±9.3 μg/day, total DA – 400.2±14.6 μg/day; which is 13.3% (1.13-fold), 7.9% (1.08-fold), 10.5% (1.1-fold) ($P<0.05$) higher than the control indicators, respectively. As for the group of RA patients infected with COVID-19, the indicators also did not differ significantly and amounted to: free DA – 197.5±9.7 μg/day, conjugated DA – 194.2±9.1 μg/day, total DA – 391.7±13.4 μg/day; which is respectively 10.1% (1.1 times), 5.5% (1.06 times), 8.2% (1.08 times) ($P<0.05$) higher than the control indicators, which showed statistically unreliable results.

Discussion. A significant decrease in the activity of blood monoamine oxidase in patients with post-COVID rheumatoid arthritis was revealed (57.1% (2.3 times) lower than the indicators of the control group and 40% (1.67 times) lower than the indicators of patients with rheumatoid arthritis, with the maximum increased daily excretion of catecholamines and their final metabolite vanillyl-mandelic acid. Correlation analysis between the excretion of catecholamines, vanillyl-mandelic acid and the activity of monoamine oxidase in patients pointed out negative feedback. Inhibition of monoamine oxidase activity with increased activity of the sympathetic-adrenal system is associated with increased lipid peroxidation processes.

Conclusion. According to the results of the study, a significant intensification of lipid peroxidation processes in patients with post-COVID rheumatoid arthritis was noted, manifested by an increased level of Adrenaline amounting to 7.9±0.7 nmol/ml, which is 1.52 times more in relation to the indicators of the group of patients with rheumatoid arthritis and almost 2.5 times more in relation to the indicators of the control group. This, in turn, contributes to the development and aggravation of oxidative stress and a sharp decrease in the body's antioxidant defense. Studies of the circadian rhythm of excretion of catecholamines epinephrine and noradrenaline in patients with post-COVID rheumatoid arthritis revealed a certain regularity, which was expressed in a decrease in the difference between the level of morning, afternoon and night excretion, with a relative increase in the level of catecholamine excretion during the night hours of observation, when compared with healthy ones

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