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CYTOMEGALOVIRUS AND VIRUS EPSTEIN- BARR INFECTION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ITS DEPENDENCE ON GENDER AND AGE OF PATIENTS

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ABSTRACT

Introduction. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by various manifestations and clinical course, many aspects of the etiology and pathogenesis of which remain unclear. Recently, the interest of researchers in studying the role of cytomegalovirus (CMV) and Epstein - Barr virus (EBV) has been growing in the occurrence and course of a number of human diseases due to their ability to affect almost all organs and systems of the body, causing the formation of latent, active or chronic infection, which can often cause temporary disability, disability or even death, however, for the patients with SLE, despite the possibility of approaching the difficult problem of diagnosis and treatment of this disease, this issue is given insufficient attention, as evidenced by isolated studies.

The aim of the study. Detect cytomegalovirus and Epstein - Barr infection in patients with systemic lupus erythematosus and its dependence on gender and age of patients.

Materials and methods of research. The study involved 120 patients (15 men (12.50%) and 105 women (87.50%) aged 18 to 69 years with SLE, who were in the rheumatology department of the Communal Non-Commercial Enterprise of the Lviv Regional Council "Lviv Regional Clinical Hospital" in 2014-2019. To diagnose CMV and EBV infection by enzyme-linked immunosorbent assay, antibodies of IgM and IgG to viruses were detected in blood serum, and viruses were detected by polymerase chain reaction. According to the results of virus detection, formed groups of the patients, namely: patients with active CMV infection, active EBV, active CMV and EBV, without active CMV and EBV. All patients with SLE included in the study were subsequently stratified by age according to the classification of the World Health Organization (2015), according to which the following age limits were determined: young age, middle-aged, elderly, senile. Statistical analysis was performed on a personal computer in MS Excel and Statistica 6.0 using descriptive statistics. The frequency of cases of active CMV and EBV infection was calculated mathematically by the binomial coefficient of I. Newton.

Research results and their discussion. We found in the vast majority of patients with SLE (117 patients, 97.50%) increase in the titer of specific antibodies to CMV. Only in 3 patients (2.50%) the titer of antibodies to this virus was within normal limits. Analyzing the frequency of EBV infection in patients with SLE, we recorded an increase in the titer of specific antibodies to the virus in 119 patients (99.17%). Among the examined patients with SLE in all (100.00%) found an increase in the titer of antibodies to CMV and / or EBV, of which 97.50% - infected with CMV and 97.17% - infected with EBV. The active phase of CMV and / or EBV infection was detected in 54.17%, of which 23.33% - active CMV infection, 17.50% - active EBV infection and 12.50% - a combination of active CMV and EBV infection simultaneously, which indicates a high frequency of CMV and EBV infection in patients with SLE and reflects the urgency of the problem of diagnosing herpesvirus infection in them. We found that active

CMV, EBV infections and their combinations are present only in women (64 patients, which is 60.96% of the total number of women with SLE), of which 28 patients (26.67%) there was only active CMV infection, in 21 patients (20.00%) - only active EBV infection and in 15 patients (14.29%) – combination of active CMV and EBV infection. 41 women (39.05%) and all (100.00%) men were not found to have active CMV and EBV infection, which indicates that men at the time of the survey were significantly more likely to have this infection in the integration phase. The most frequently active EBV infection was detected in patients with SLE of young age (17 cases, 24.64%), and in middle-aged patients 3 cases (6.52%) were recorded, which indicates a significant ($p < 0.05$) difference in the frequency of cases of active EBV infection in patients of both groups. Only 1 case (20.00%) of active EBV infection was detected in elderly patients.

Conclusions. All patients with systemic lupus erythematosus are infected - 97.50% with cytomegalovirus and 97.17% with Epstein-Barr virus infection, that was confirmed by the increased titer of antibodies to them. Among the mentioned patients 53.33% of them had the active phase of infection (23.33% - cytomegalovirus infection in the replication phase, 17.50% - the Epstein- Barr virus infection in the replication phase and 12.50% - their combination).

The prevalence of active viral infection in patients with systemic lupus erythematosus depends on gender (active cytomegalovirus, active Epstein-Barr virus infection and their combination are significantly more common in women) and age - they are probably more common in young patients.

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Introduction. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by various manifestations and clinical course, many aspects of the etiology and pathogenesis of which remain unclear. Recently, the interest of researchers in studying the role of cytomegalovirus (CMV) and Epstein - Barr virus (EBV) in the occurrence and course of a number of human diseases due to their ability to affect almost all organs and systems of the body, causing the formation of latent, active or chronic infection, which can often cause temporary disability, disability or even death has been growing [4, 5]. However, these viruses in the patients with SLE, despite the possibility of approaching the difficult problem of diagnosis and treatment of the main disease, are not sufficiently studied, as evidenced by only isolated studies [1, 2, 3].

The aim of the study. Detect cytomegalovirus and Epstein – Barr virus infection in patients with systemic lupus erythematosus and its dependence on gender and age of patients.

Materials and methods of research. In a randomized way with the preliminary stratification by SLE, established based on the diagnostic criteria of the American College of Rheumatology (ACR, 1997), 120 patients (15 men (12.50%) and 105 women (87.50%) aged 18 to 69 years, who were treated in the rheumatology department of the Communal Non-Commercial Enterprise of the Lviv Regional Council "Lviv Regional Clinical Hospital" in 2014-2019 were involved to the study.

CMV and EBV infection was diagnosed using enzyme-linked immunosorbent assay, immunoglobulin M antibodies (Immunoglobulin M - IgM) and immunoglobulin G antibodies (Immunoglobulin - IgG) to viruses were detected in blood serum, as well as viruses were detected (CMV – urine, blood; EBV - mucous membranes of the oral cavity, blood) by polymerase chain reaction.

According to the results of virus detection, the groups of patients were formed, namely: patients with active CMV infection (increased IgM to CMV and detection of deoxyribonucleic acid (DNA) virus), active EBV (increased IgM to EBV and virus DNA detection), active CMV and EBV (increase in IgM content to CMV and EBV, virus DNA detection), without active CMV and EBV (IgM to viruses were within reference values, no virus DNA detected). All patients with SLE included in the study were subsequently stratified by age according to the classification of the World Health Organization (2015), according to which the following age limits were determined: young age (from 18 to 44 years), middle-aged (from 45 to 59 years)), elderly (from 60 to 74 years), senile (75-89 years).

To achieve the goal of the study, we took three steps: the first step was to analyze the CMV and EBV infection in patients with SLE; the second - the analysis of CMV and EBV infection in

patients with SLE depending on gender; third - the analysis of CMV and EBV infection in patients with SLE depending on the age of patients.

Statistical analysis was performed on a personal computer in MS Excel and Statistica 6.0 using descriptive statistics. The frequency of cases of active CMV and EBV infection was calculated mathematically by the binomial coefficient of I. Newton.

Research results and their discussion. First step. In accordance with the aim of the study, analyzing CMV infection in patients with SLE, we found (Table 1, Fig. 1) that in the vast majority of patients with SLE (117 patients, 97.50%) the titer of specific antibodies to CMV was increased. The titer of antibodies to this virus was within the normal limits only in 3 patients (2.50%). Among the patients with SLE with the increased titer of antibodies to CMV, we recorded the IgM antibodies titer increase, which may indicate an acute phase of infection (primary infection, chronic infection exacerbation, or reinfection) in 43 patients (36.75%), namely: 38 patients - simultaneous IgM and IgG antibodies and in 5 patients - only IgM antibodies titer increase.

The rest (74 patients, 63.25%) showed an increase of only the IgG antibodies titer, which may be a sign of infection or the immunity to it ("immune memory").

Table 1. Frequency of detection of antibodies to cytomegalovirus in patients with systemic lupus erythematosus (n; %)

Name of antibodies to CMV	Number of patients, n = 117	
	absolute amount, n	%
IgM antibodies to CMV	43	36.75
IgG antibodies to CMV	74	63.25

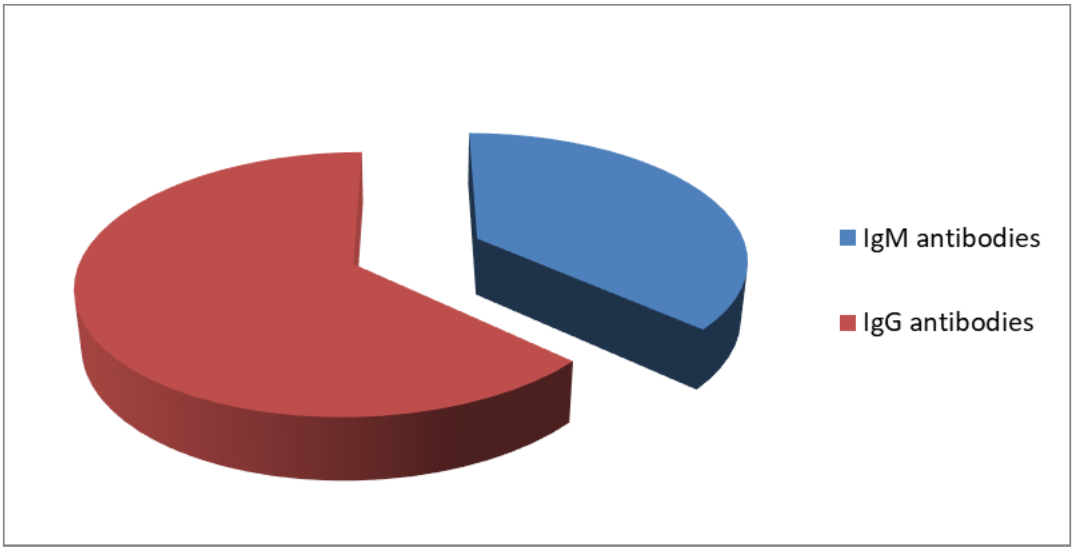

Fig. 1. Frequency of detection of antibodies to CMV in patients with SLE

Analyzing the frequency of EBV infection in patients with SLE (Table 2, Fig. 2), we recorded the increase of the specific viral antibodies titer in 119 patients (99.17%), namely: the increase of the IgM to viral capsid antigen (VCA) EBV titer, appearing in the acute phase of the disease or in the exacerbation phase, was recorded in 36 patients with SLE (30.25%), in the remaining 83 patients (69.75%) the titer of IgM antibodies to VCA EBV was within the normal limits.

Table 2. The frequency of antibodies to Epstein-Barr virus detection in patients with systemic lupus erythematosus (n; %)

Name of antibodies to EBV	Number of patients, n = 119	
	absolute amount, n	%
Antibodies to IgM VCA EBV +	36	30.25
Antibodies to IgM VCA EBV -	83	69.75

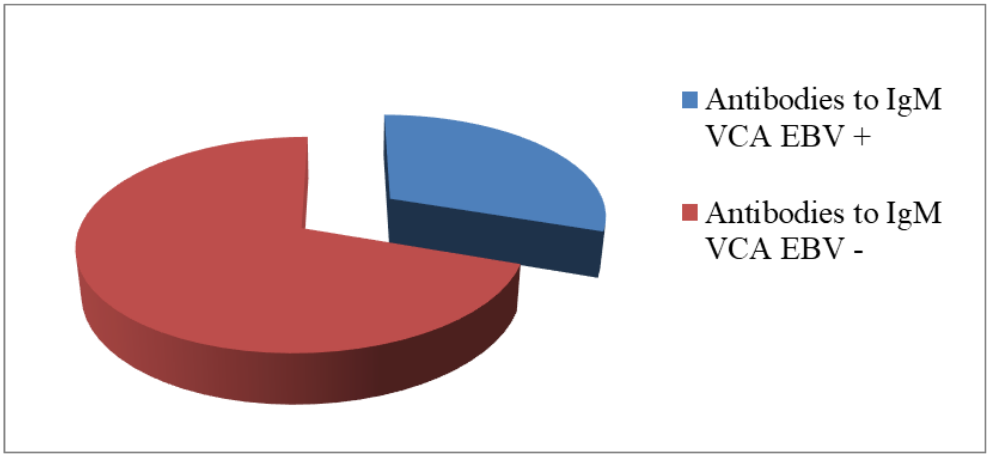

Fig. 2. Frequency of detection of antibodies to EBV in patients with SLE

The increase of the IgG antibodies to early antigen (EA) titer, being a marker of active replication of the virus, was found (Table 3) in 82 patients (68.91%), and IgG antibodies to nuclear antigen (NA) (produced throughout life) titer increase, usually detected 2-4 months after the acute phase was found in 118 patients (99.16%).

Table 3. Frequency of Epstein-Barr virus various markers detection in patients with systemic lupus erythematosus (n; %)

Name of EBV markers	Number of patients, n = 119	
	absolute number, n	%
Antibodies to IgM VCA EBV	36	30.25
Antibodies to IgG EA EBV	82	68.91
Antibodies to IgG NA IgG	118	99.16

In general, we found (Table 4 and Fig. 3) that 28 patients with SLE (23.33%) had active CMV infection and 21 patients (17.50%) had active EBV infection. In 15 patients with SLE (12.50%) a combination of active CMV and EBV infection was detected. The active CMV and/or EBV was not found in the remaining 56 patients with SLE (46.67%), only the increase of the CMV/ EBV IgG antibodies content was detected.

Table 4. Frequency of active cytomegalovirus and/or Epstein – Barr virus infection detection in patients with systemic lupus erythematosus (n; %)

Phase of CMV and/or EBV infection	Number of patients, n = 120	
	absolute amount, n	%
Active CMV infection	28	23.33
Active EBV infection	21	17.50
Active CMV and EBV infection	15	12.50
No active CMV and EBV infection	56	46.67

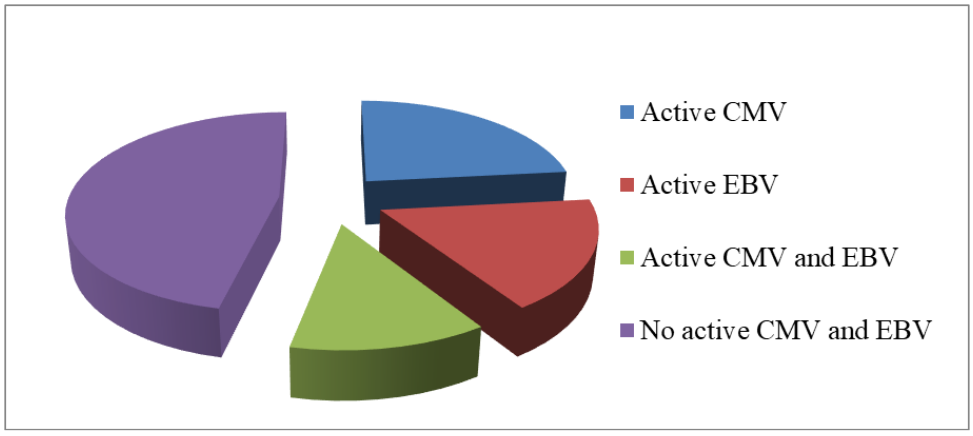

Fig. 3. Frequency of detection of active CMV and/or EBV infection in patients with SLE

Thus, among the examined patients with SLE in all (100.00%) of them we found the increased titer of antibodies to CMV and/or EBV, among which 97.50% - infected with CMV and 97.17% - infected with EBV. The active phase of CMV and/or EBV infection was detected in 54.17%, 23.33% of them - active CMV infection, 17.50% - active EBV infection and 12.50% - combination of active CMV and EBV infection. This fact indicates a high frequency of CMV and EBV infection in patients with SLE and reflects the herpesvirus infection diagnosis problem urgency in them.

The results of the second step of our study, which is devoted to determining the prevalence of CMV and EBV infection by gender, are shown in the Table 5.

Table 5. Features of cytomegalovirus and Epstein-Barr virus infection depending on the gender of patients with systemic lupus erythematosus (n; %; p)

Phase of CMV infection and / or EBV infection	Patients with systemic lupus erythematosus			
	Women, n = 105		Men, n = 15	
	n	%	n	%
Active CMV infection	28	26.67	0	0.00
Active EBV infection	21	20.00	0	0.00
Active CMV and EBV infection	15	14.29	0	0.00
No active CMV and EBV infection	41	39.05	15	100.00

We found that active CMV, EBV infections and their combinations were present only in women (64 patients, which is 60.96% of the total number of women with SLE), 28 patients (26.67%) of which had only active CMV infection, 21 patients (20.00%) - only active EBV infection and 15 patients (14.29%) – combination of active CMV and EBV infection. 41 women (39.05%) and all (100.00%) men were not found to have active CMV and EBV infection, which indicates that men at the time of the study were significantly more likely to have this infection in the integration phase.

The results of the third step of this study, which aims to determine the frequency of CMV and EBV infection depending on the patient's age, are shown in the Table 6.

Table 6. Features of the active cytomegalovirus and Epstein-Barr infection determination depending on the age of patients with systemic lupus erythematosus (n; %; p)

Phase of CMV infection and / or EBV infection	Age of patients with SLE					
	Young patients, n = 69		Middle-aged patients, n = 46		Elderly patients, n = 5	
	n	%	n	%	n	%
Active CMV infection	21	30.43	7*	15.22	0	0.00
Active EBV infection	17	24.64	3*	6.52	1	20.00
Active CMV and EBV infection	10	14.49	5	10.87	0	0.00
No active CMV and EBV infection	21	30.43	31	67.39	4	80.00

Note. * - statistically confirmed difference with the number of cases in young patients ($p < 0.05$).

According to the information presented in the Table 6, the number of cases with active CMV infection was significantly ($p < 0.05$) more common (21 cases; 30.43%) in young patients with SLE. Slightly less cases of this infection were detected among the middle-aged patients (7 cases; 15.22%), and no cases of active CMV infection were detected in elderly patients (0.00%).

The most frequently active EBV infection was detected in young patients – 17 cases (24.64%), and in middle-aged patients - 3 cases (6.52%; $p < 0.05$). Only one case (20.00%) of active EBV infection was detected in elderly patients.

Active CMV, combined with active EBV infection, was the most often diagnosed in young patients with SLE (10 cases; 14.49%), less often in patients with SLE of the middle age (5 cases; 10.87%) and was not detected in elderly patients. However, we did not find a significant difference between the incidence of active CMV and EBV infection in patients with SLE of different ages ($p > 0.05$).

According to our information active CMV, active EBV infection and a combination of active CMV and EBV infection are most common in patients with SLE aged 18 to 44 years.

Conclusions. All patients with systemic lupus erythematosus are infected - 97.50% with cytomegalovirus and 97.17% with Epstein-Barr virus infection, that was confirmed by the increased titer of antibodies to them. Among the mentioned patients 53.33% of them had the active phase of infection (23.33% - cytomegalovirus infection in the replication phase, 17.50% - the Epstein - Barr virus infection in the replication phase and 12.50% - their combination).

The prevalence of active viral infection in patients with systemic lupus erythematosus depends on gender (active cytomegalovirus, active Epstein-Barr virus infection and their combination are significantly more common in women) and age - they are probably more common in young patients.

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