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Endotoxin Is a Component in the Pathogenesis of Chronic Viral Diseases

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Abstract—The level of endotoxin and indicators of the activity of anti-endotoxin immunity (the concentration of antibodies against *Re* chemotype glycolipid and enterobacterial common antigen) were determined in the serum of 174 patients with persistent viral infections (with herpes simplex, hepatitis C, and human immunodeficiency viruses). In HIV-infected patients, the presence of markers of the systemic inflammatory response syndrome (interleukin IL-1α) and acquired immunodeficiency (CD4 +) was also determined. Persistent viral infections have been found to be accompanied by endotoxin aggression of intestinal origin, which they cause themselves and which can induce the systemic inflammatory response syndrome. In HIV-infected patients, this syndrome is cyclic, the phase of hyperactivity alternating with immunodeficiency. Schematically, this process can be represented as the following sequence of events: HIV-mediated damage to the intestinal barrier–development of endotoxin aggression–induction the of systemic inflammatory response syndrome–immune exhaustion, which is transient and related to the duration of the virus replication cycle, i.e., with the damage to enterocytes. The use of the anti-endotoxin component (a tool for reducing the levels of endotoxin in blood) in the scheme of treatment for persistent viral infections can contribute to successful prevention of complications.

Keywords: lipopolysaccharide, endotoxin aggression, viral iridocyclitis, chronic hepatitis C, HIV infection, systemic inflammatory response syndrome, acquired immunodeficiency syndrome

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Viral infections underlie the development of many chronic diseases, including those resulting in disablement and untimely death. Unfortunately, the current approaches to the therapy for persistent infections and associated complications not always take into consideration the role of some nonspecific general factors in the pathogenesis of viral diseases, though the quality of therapeutic process can be potentially enhanced by influencing these factors. One of these factors may be intestinal endotoxin (IE), or rather endotoxin aggression (EA). We took note of this aspect of viral pathogenesis for the first time about 25 years ago, when examining children with viral respiratory infections [1] demonstrating a direct interrelationship between the concentration of intestinal lipopolysaccharides (LPS) in blood serum and the development of the bronchial obstruction syndrome, which is probably connected with enhanced intestinal permeability developing against the background of viral infection. In this connection, we continued the studies in this direction with the purpose to find out a relationship of clinically manifested long-term persistent viral infections and their complications with the integrated indices of systemic endotoxemia (SE).

METHODS

Blood samples from three groups of patients with different chronic viral infections were studied in accordance with the requirements of the Local Ethics Committee.

Group 1 (iridocyclitis): 109 in-patients of both sexes, 24 to 79 years old ($M \pm SD = 51 \pm 1$), undergoing therapy at the Moscow Ophthalmological Clinical Hospital and at the Institute of General and Clinical Pathology (Clinical Diagnostic Society of the Russian Academy of Natural Sciences) in the period from 2001 to 2011. The group included 47 patients with herpes virus iridocyclitis (acute, 23; recurrent, 24) and 62 patients with nonviral (unidentified etiology) anterior uveitis (acute, 25; recurrent, 34); the data were used as one of the control groups. The basic anti-endotoxin component (AEC) was added to the currently accepted (standard) therapeutic scheme used

Table 1. The integrated indices of systemic endotoxemia in the patients with iridocyclites of different etiology compared to the age-related norm

No.	Uveitis type	Concentration in blood serum, *Me* [25–75%]		
		LPS, EU/mL	anti-GLP ABs, RODU	anti-ECA ABs, RODU
1	Viral, $n = 47$	2.49 [2.0–3.0]	128 [112–143]	287 [245–316]
2	Of unknown etiology, $n = 62$	3.17 [2.5–3.5]	133 [110–167]	299 [227–350]
	p between groups 1 and 2	0.02	>0.05	>0.05
3	Age-related norm	0.94 [0.6–1.0]	147 [145–153]	292 [279–321]
	p between groups 1 and 3	<0.001	>0.05	>0.05
	p between groups 2 and 3	<0.001	>0.05	>0.05

Here and in Tables 2–9: abbreviation expansions see in the "Methods."

for all patients. The values typical of the age group of 52–60 years were used as standard indicators of SE.

Group 2 (chronic viral hepatitis C (CVHC)): the study was carried out in blood serum from 31 CBHC in-patients of both sexes but mostly men, 22 to 52 years old, undergoing therapy at the Institute of General and Clinical Pathology (Clinical Diagnostic Society of the Russian Academy of Natural Sciences). AEC was added to the current therapeutic scheme.

Group 3 (HIV-infected patients, including those with AIDS): blood samples were taken from 96 patients at different clinical stages of the disease (from 3 to 4b) and ranked according to the concentration of interleukin-1β (IL-1β); 21 patient with very high (above 100 pg/mL, $n = 11$) and low (below 11 pg/mL, $n = 10$) IL-1β concentrations was selected among them. This selection (and the respective groups) of patients is in agreement with comparison of the two strictly antipodal points of development of the systemic inflammatory response syndrome (SIRS): a "hyperactivation peak" and an "exhaustion peak", the quantity of each being about 11% of the total number of patients.

The treatment regimen for patients from groups 1, 2 and, partially, 3, in addition to the currently accepted therapy, included AEC, i.e., the preparations and procedures for reducing the LPS concentration in general circulation (basic AEC: enterosorbents, eubiotics, cholagogues, diuretics).

The total LPS concentration was determined by the *LAL* test (using *E-toxate* reagent and LPS reference standard, Sigma) in our clinically adapted modification based on the ability of *LAL* reagent to form fractal proteins when contacting ET. The activity of anti-endotoxin immunity (AEI) was comprehensively assessed by measuring the concentration (in relative optical density units, RODU) of antibodies (ABs) against the most common antigens of the LPS molecule: *Re* chemotype glycolipid (GLP), which is a component of all ETs and is responsible for the common spectrum of biological properties of LPS, and enterobacterial common antigen (ECA) by the SOIS-IFA technique (Clinical Diagnostic Society). The etiology of EA was determined by the serological method (enzyme immunoassay) only in CVHC patients and was considered as ascertained, if the concentration of ABs against the Gram-negative bacterium was threefold higher than the upper limit of the norm or, respectively, was three times lower than the lower limit of the norm.

The Statistica software version 6.0 (StatSoft, United States) was used for statistical processing of the data. Since most of the indices studied had no approximately normal distribution, all data are presented as median and interquartile ranges: *Me* [25%–75%]. The significance of differences between independent samples was estimated by the nonparameteric Mann-Whitney test; the significance of differences between dependent samples (the groups before and after the treatment) was estimated by the nonparametric Wilcoxon *W* test. The critical level of significance of differences was taken to be ≤0.05.

RESULTS AND DISCUSSION

HSV uveitis. We considered this disease to be the most suitable for studying the supposed role of EA in viral pathogenesis, since the efficiency of therapeutic process (including AEC) can be rather objectively assessed by a very simple indicator, namely recurrence rate.

Our study showed that ET concentration in blood serum of the overwhelming majority (98%) of patients with iridocyclitis (both viral and nonviral) was substantially higher compared to the group of the age-related norm [2]; in the absence of increase in the integrated indices of AEI, this leads to the conclusion about chronic EA in the patients with uveitis (Table 1).

This fact seems to be important, since it is known that parenteral administration of LPS to different experimental animals induces the development of uveitis [3]. A no less interesting fact is that iridocyclitis in HSV-infected patients develops at much lower ET concentrations in blood serum compared to the

Table 2. The dynamics of integrated indices of systemic endotoxemia in the patients with anterior uveitis as a result of therapy

No.		Concentration in blood serum, *Me* [25–75%]		
		LPS, EU/mL	anti-GLP ABs, RODU	anti-ECA ABs, RODU
1	Age-related norm	0.94 [0.6–1.0]	147 [145–153]	292 [279–321]
2	Viral, $n = 47$			
2.1	Before treatment	2.49 [2.0–3.0]	128 [112–143]	287 [245–316]
2.2	After treatment	1.19 [1.0–1.25]	179 [175–195]	374 [365–392]
p between 2.1 and 2.2		<0.001	0.02	0.01
p between 2.2 and the normal value		0.03	0.04	0.001
3	Of unknown etiology			
3.1	Before treatment	3.17 [2.5–3.5]	133 [110–167]	299 [227–350]
3.2	After treatment	1.45 [1.0–2.0]	179 [175–195]	372 [358–395]
p between 3.1 and 3.2		0.003	0.03	0.02
p between 3.2 and the normal value		0.01	0.02	0.03
p between 2.2 and 3.2		0.01	>0.05	>0.05

patients with this disease of unidentified etiology (2.49 [2.0–3.0] and 3.17 [2.5–3.5] *EU/mL*, $p = 0.02$). All patients received extended treatment including, in addition to the conventional therapy, the basic AEC supplemented with intravenous laser blood irradiation (increasing the activity of AEI), gentamycin (with the LPS-binding effect), and antiviral drugs. The dynamics of changes in the mean indices of SE as a result of treatment with AEC is shown in Table 2 and Fig. 1.

As a result of this course of treatment, the LPS concentration in blood serum of the patients significantly decreased (from 2.49 [2.0–3.0] to 1.19 [1.0–1.25] *EU/mL*, $p < 0.001$ for viral uveitis; from 3.17 [2.5–3.5] to 1.45 [1.0–2.0] *EU/mL*, $p = 0.003$ for unidentified uveitis) and the integrated indices of AEI activity increased (for viral uveitis: anti-GLP ABs, from 128 [112–143] to 179 [175–195] RODU, $p = 0.02$; anti-ECA ABs, from 287 [245–316] to 374 [365–392] RODU, $p = 0.01$; for uveitis of unidentified etiology: anti-GLP ABs, from 133 [110–167] to 179 [175–195] RODU, $p = 0.03$; anti-ECA ABs, from 299 [227–350] to 372 [358–395] RODU, $p = 0.02$), which we did not observe in the case of the currently accepted therapy [4].

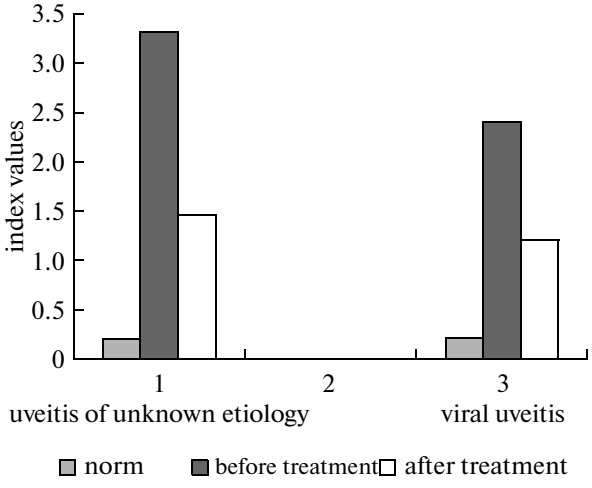

Fig. 1. The dynamics of endotoxin concentration in blood of the patients with iridocyclites as a result of therapy with the anti-endotoxin component. HSV infection considerably reduces the pathogenic concentration of lipopolysaccharides in uveites.

The comparison of the efficacy of treatment for the conventional and "extended" therapeutic regimens by recurrence rate showed that AEC decreased it by a factor of five. Hence, we decided to analyze how much the iridocyclitis recurrence rate would decrease during 12 months after the completion of the course of treatment compared to the initial value (1.54 ± 0.14 per year, according to the case history). It decreased by more than an order of magnitude. Recurrence was observed in only two patients: one patient (2.1%) with viral iridocyclitis (against a background of severe influenza) and one patient (1.6%) with uveitis of unidentified etiology (against a background of long-term exposure to stress while on duty). The results were even more indicative in the subgroup of patients with recurrent iridocyclitis (24 subjects with viral uveitis and 35 subjects with uveitis of unidentified etiology), who repeatedly underwent in-patient treatment. In this group, recurrence rate decreased by factors of no less than 12 and 15, respectively (Fig. 2).

Thus, the use of AEC in the therapeutic regimen for HSV uveitis reduces the recurrence rate 12 times,

allowing us to assert the involvement of EA in the pathogenesis of viral iridocyclitis.

Chronic viral hepatitis C (CVHC). This study showed that none of the CVHC patients had SE indices corresponding to the age-related norms (see Table 3).

The median of LPS concentration in CVHC patients exceeded the normal values nearly fivefold (3.03 [2.5–3.5], with the normal value of 0.67 [0.3–1.0] *EU/mL*), in the fluctuation range (from 1.25 to 6.25 *EU/mL*) of values many times higher than the normal values. These patients are characterized by a very broad range (both upward and downward) of concentrations of ABs against both GLP and ECA. In spite of this circumstance, the mean values of anti-ECA ABs in CVHC patients were considerably higher than the normal values. This suggests transitory insufficiency of the intestinal barrier in CVHC patients, which may be a direct consequence of virus-induced damage of the mucous membrane. This is indirectly confirmed by the data given in Tables 4 and 5.

The sources of EA were found in 29 out of 31 CVHC patients. Bacteroides proved to play a certain role in the overwhelming majority of these patients, being the only source of EA in 58% (18 CVHC patients), while the LPS of other three Gram-negative bacteria (proteus, coliform and blue pus bacilli) were involved in EA formation three times less frequently. If we assume that the major cause of EA development is virus-induced transitory insufficiency of the intestinal barrier, this fact can be quite logically accounted for by a substantially (many times) larger total population of bacteroides in the intestines compared to other Gram-negative bacteria.

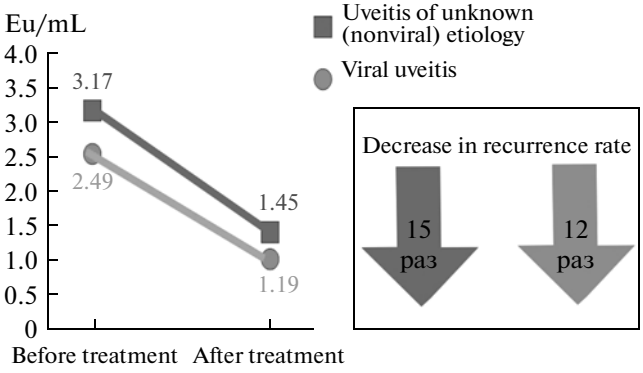

Fig. 2. The efficiency of anti-endotoxin component in the therapy for patients with viral iridocyclitis and iridocyclitis of unknown etiology.

The treatment regimen that we have developed to reveal the role of EA in the pathogenesis of CVHC includes three 10-day courses (at 20-day intervals): a protease inhibitor (Virolex, intravenously, no. 10), Polyoxidonium (6 mL intravenously, no. 10), and AEC ("Heptral", 400 mg, intravenously; concentrated bifidobacteria, 1 flask, before the breakfast and before the sleep; "Kipferon", rectally, 2 times per day). In addition, between the courses concentrated bifidobacteria (twice a day) were administered to all patients from groups 1 (without laboratory signs of cytolysis) and 2 (with laboratory signs of cytolysis); "Ferrovir" (intramuscularly, 14 days) was also administered to the patients from group 2. The therapy made it possible to achieve a virologic response (negative polymerase chain reaction result) in almost 75% and 50% patients

Table 3. The integrated indices of systemic endotoxemia in the patients with chronic viral hepatitis C (CVHC) compared to the age-related norm

		Concentration in blood serum		
		LPS, EU/mL	anti-GLP ABs, RODU	anti-ECA ABs, RODU
1	CVHC patients, $n = 31$			
1.1	Range of indicators	1.25–6.25	28–420	163–691
1.2	*Me* [25–75%]	3.03 [2.5–3.5]	184 [120–232]	409 [314–512]
2	Age norm			
2.1	Range of indicators	0.3–1.25	130–200	325–400
2.2	*Me* [25–75%]	0.67 [0.3–1.0]	164 [153–171]	347 [330–367]
p		<0.001	NS	0.04

Table 4. The frequency of involvement of endotoxin of Gram-negative bacteria in the development of endotoxin aggression in CVHC patients

Source of endotoxin aggression	Patients with chronic viral hepatitis C	
	number of patients	percentage of participation
Bacteroides	29	93.5%
Proteus	11	35.5%
E. coli	11	35.5%
Pseudomonas aeruginosa	11	35.5%
Klebsiella	0	0%
Unidentified source	2	6.5%

Table 5. The number of etiological factors of the development of endotoxin aggression in CVHC patients

	Number of identified etiological factors of endotoxin aggression development					
	0	1	2	3	4	5
Number of patients	2	18	6	3	2	0
Percentage of patients	6.5%	58%	19.5%	9.5%	6.5%	0%

Table 6. The antiviral efficiency of therapeutic scheme for CVHC patients

Groups of CVHC patients, number of patients in a group	The presence of viremia in CVHC patients	
	before the treatment course	after the treatment course
First group, $n = 11$	11/100%	3/27.3%
Second group, $n = 20$	20/100%	11/55%
Combined group, $n = 31$	31/100%	14/45.2%

from groups 1 and 2 (with considerable improvement of biochemical indices), respectively, which was also accompanied by a positive dynamic of changes in SE values (Table 6, Fig. 3).

As a result of this therapy, the LPS concentration in blood serum was considerably (three times) decreased (from 3.03 [2.5–3.5] to 1.0 [0.6–1.25] *EU/mL*, $p < 0.001$) in all CVHC patients (Table 7, Fig. 4), with a substantial decrease in the content of anti-ECA ABs in blood (from 409 [369–416] to 347 [292–386], $p = 0.03$), demonstrating a reduced influx of intact ET molecules (the hydrophilic form of LPS) from the intestines, which is most probably determined by intestinal barrier damage.

Thus, it seems possible to assume that EA is one of the factors of CVHC pathogenesis; at the same time, its development may be caused by enhanced intestinal permeability, most probably, due to virus-induced damage of gastrointestinal mucosa which has not been supposed previously (by our predecessors).

HIV infection. As has been reported in the literature in recent years, the intestinal factor is probably involved in the pathogenesis of HIV infection [5–7]. For example, the clinical studies of G.R. Khasanova et al. [8, 9] (a group of 232 outpatients at the Republican Center for AIDS and Infectious Disease Prevention and Control, Ministry of Health of the Republic of Tatarstan, Kazan) convincingly showed the involvement of EA of intestinal origin in HIV-induced hyperactivation of the immune system. In particular, a direct correlation between the concentrations of LPS and IL-1β in general circulation has been revealed, which demonstrates that EA is the primary cause of SIRS induction. At the same time, the causes of the undulating clinical course of HIV infection and the possibility of ET involvement in the latter are still open questions.

We attempted to answer this question by determining in the blood of patients, in addition to the integrated indices of SE, the concentration of *CD*4+ cells (as a marker for immunosuppression), hemoglobin, erythrocyte sedimentation rate (ESR), red blood count (RBC), the number of mature circulating myeloid cells, and viral load.

The values given in Table 8 suggest that the patients at the third stage of HIV infection have no SIRS exhaustion phase (in the predetermined parameters) but exhibit hyperactivation of the immunity, which is

evidence of the initial phase of SIRS development when the reserve capacity of the immune system is yet sufficiently high, whereas the situation for patients with more severe stages of the disease is opposite.

The results of laboratory studies in the two groups of HIV patients that we had selected, in spite of their small numbers, confirmed the accuracy of the previous data of G.R. Khasanova et al. [8, 9] and allowed us to obtain quite a number of new important reliable facts (Table 9).

The highly important difference between the groups of comparison is much (2.5 times) lower concentrations of *CD*4+ in patients in the phase of SIRS exhaustion compared to patients in the phase of SIRS activation (136.5 [59–158] and 379 [279–576], respectively, $p = 0.002$), demonstrating the validity of dividing patients into the corresponding samples. This is also confirmed by other facts: the patients of this group have leukopenia (2.6 [1.9–4.0] vs. 4.7 [4.6–6.1], $p = 0.006$) and anemia, which is characterized by the lower RBC values (3.16 [2.96–3.93] vs. 4.37 [3.77–4.52], $p = 0.01$) and hemoglobin concentration (96 [81–111] vs. 116 [111–118], $p = 0.004$). In addition, the patients from the group with SIRS exhaustion are characterized by much (2.5-fold) higher ESR values (47 [42–60] and 19 [8–28], $p = 0.003$) compared to the patients from the group with hyperactivation. Finally, there are two more new and very important facts: the levels of viral load in the compared groups are not significantly different, with a considerable (tenfold) difference in LPS concentration in the general circulation (0.45 [0.19–1.21] and 4.84 [3.84–6.09], $p = 0.0003$); the phase of exhaustion is accompanied by the activation of the myelocytic process of bone marrow; i.e., the number of stab granulocytes considerably increases (4.5 [2–8] and 0, respectively, $p = 0.001$), indicating the completion of one SIRS cycle and the beginning of the next cycle (Fig. 5).

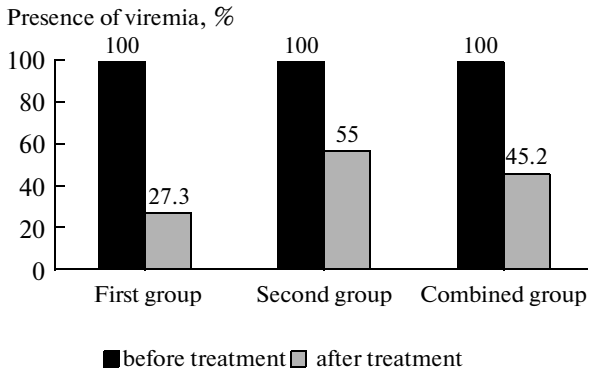

Fig. 3. The efficiency of therapy for patients with chronic viral hepatitis C (by elimination of viremia) using the anti-endotoxin component.

Thus, HIV infection is accompanied by the development of EA, which is detected at all clinical stages of the disease and most probably determined by the direct damaging effect of HIV on the intestinal barrier.

Table 7. The dynamics of integrated indices of systemic endotoxemia in CVHC patients as a result of therapy

	CVHC patients, number in a group	Concentration in blood serum, *Me* [25–75%]		
		LPS, EU/mL	anti-GLP ABs, RODU	anti-ECA ABs, RODU
1	First group, $n = 11$			
1.1	Before treatment	2.68 [2.0–3.0]	220 [152–255]	442 [369–519]
1.2	After treatment	0.72 [0.6–1.0]	196 [163–246]	393 [369–416]
p		<0.001	NS	NS
2	Second group, $n = 20$			
2.1	Before treatment	3.23 [2.5–3.5]	165 [112–218]	391 [290–476]
2.2	After treatment	1.16 [0.6–1.5]	143 [105–230]	322 [270–371]
p		<0.001	NS	0.04
Combined group, $n = 31$				
Before treatment		3.03 [2.5–3.5]	184 [120–232]	409 [369–416]
After treatment		1.0 [0.6–1.25]	162 [122–193]	347 [292–386]
p		<0.0001	NS	0.03

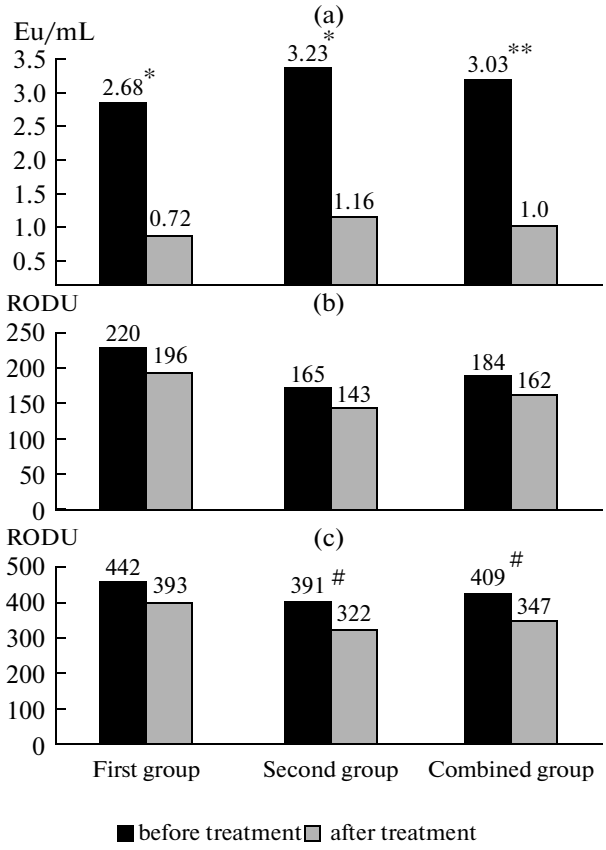

Fig. 4. The dynamics of integrated values of endotoxin concentration and the activity of anti-endotoxin immunity in the patients with chronic viral hepatitis C as a result of therapy with the anti-endotoxin component. *A*, lipopolysaccharides (LPS); *B*, antibodies against *Re* chemotype glycolipid (anti-GLP ABs); *C*, antibodies against the enterobacterial common antigen (anti-ECA ABs). *$p < 0.001$, **$p < 0.0001$, #$p < 0.05$.

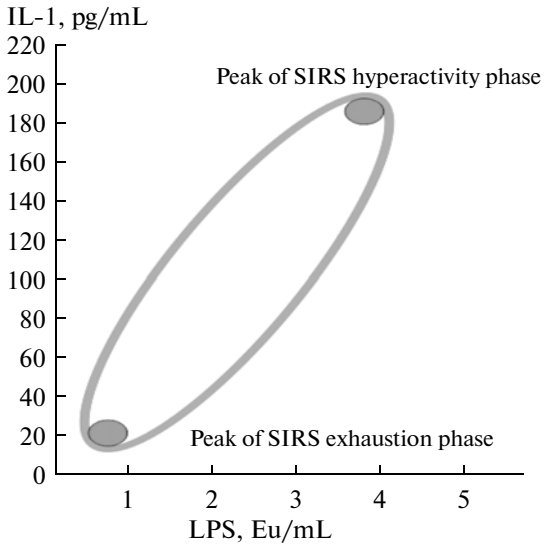

Fig. 5. The cyclicity of the systemic inflammatory response syndrome (SIRS) in HIV patients. IL-1, interkeukin-1; LPS, lipopolysacchrides.

The broad range of LPS and IL-1 concentrations can ensure the cyclic undulating course of the disease, which may have the following pattern: HIV-induced damage of the intestinal barrier (transitory)–EA development–SIRS induction–immune system exhaustion (which is manifested, inter alia, in the enhanced risk of oncology). The importance of the intestinal factor of HIV-induced pathogenesis of SIRS, both as a source of EA development and, in all likelihood, the main localization of viral replication, which cyclically determines the intestinal barrier damage (increase in permeability), is confirmed by the researchers [9] who have revealed the ability of AEC to reduce the symptoms of "anemia of chronic disease" (typical of the exhaustion phase of SIRS). We are aware that the postulated cyclicity of LPS-induced SIRS in HIV patients, which underlies AIDS, needs to be investigated by continuous laboratory monitoring of the groups of patients at different stages of disease development.

Table 8. The structure of comparison groups by the stages of HIV infection

Phases of SIRS development	Clinical stages of HIV infection development, number of patients			Total
	3	4a	4b	
Hyperactivity	7	3	1	11
Exhaustion	–	8	2	10
Total	7	11	3	21

Table 9. The comparison of indices in the two extreme phases of SIRS development

Index	Phases of SIRS development		*p*
	hyperactivity	exhaustion	
Age	27 [23–38]	32.5 [27–36]	0.38
Gender, m/f	4/7	4/6	0.78
IL-1 concentration, pg/mL	198.7 [141.4–298.2]	4.0 [0.1–10.2]	<0.0001*
LPS concentration, EU/mL	4.84 [3.84–6.09]	0.45 [0.19–1.21]	0.0003*
*CD*4+ concentration, cells/μL	379 [279–576]	136.5 [59–158]	0.002*
Concentration of anti-GLP ABs, RODU	109.5 [74.2–178.5]	258.1 [236.7–331.9]	0.006*
Concentration of anti-ECA ABs, RODU	121.6 [112.3–214.2]	142.8 [78.1–245.6]	0.9
Lymphocyte count	39 [28–42]	29.5 [22–52]	0.8
Leukocyte count	4.7 [4.6–6.1]	2.6 [1.9–4.0]	0.006*
ESR	19 [8–28]	47 [42–60]	0.003*
Viral load	1.43 [1.36–1.59]	1.5 [1.41–1.67]	0.86
Stab neutrophil count	0	4.5 [2–8]	0.001*
Segmented neutrophil count	52 [47–56]	57.5 [29–63]	0.8
Eosinophil count	1 [0–2]	0 [0–1]	0.2
Monocyte count	8 [6–12]	9.5 [6–10]	0.7
Basophil count	0	0	0.97
Erythrocyte count	4.37 [3.77–4.52]	3.16 [2.96–3.93]	0.01*
Hemoglobin concentration	116 [111–118]	96 [81–111]	0.004*
Body temperature	36.6	36.6 [36.6–37.8]	0.38

* Differences are statistically significant.

CONCLUSIONS

Persistent viral infections (caused by the herpes simplex, hepatitis C, and human immunodeficiency viruses) are accompanied by the development of endotoxin aggression of intestinal origin (also accounted for by the above viruses), which induces the development of systemic inflammatory response syndrome. In the case of HIV infection, this syndrome is cyclic. The use of the "anti-endotoxin component" in the complex therapeutic regimen for chronic infections may be an element of successful prevention of their complications.

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