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ВЛИЯНИЕ РЕАКТИВАЦИИ ВИРУСОВ ГЕРПЕСА ЧЕЛОВЕКА НА СИСТЕМНУЮ ПРОДУКЦИЮ ЦИТОКИНОВ У ПАЦИЕНТОВ С БОЛЕЗНЬЮ БЕХЧЕТА И УВЕИТАМИ

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Резюме. Болезнь Бехчета (ББ) – системное аутовоспалительно-аутоиммунное заболевание (хронический системный васкулит) невыясненной этиологии, увеит развивается почти у 70% пациентов. Патогенез ББ сложен, среди инфекционных триггерных факторов важную роль играют герпесвирусы человека (*HHV*). Известна способность *HHV* модулировать продукцию цитокинов и уклоняться от иммунного ответа организма. Цель работы: определить влияние *Herpes simplex virus type 1 (HSV-1), Herpes simplex virus type 2 (HSV-2), Cytomegalovirus (CMV), Epstein-Barr virus (EBV)* на системные уровни хемокинов, про- и противовоспалительных цитокинов при ББ с симптомами увеитов и без. Сыворотки 116 пациентов с ББ, хронически инфицированных герпесвирусами, исследовали в иммуноферментном анализе на наличие *IgG*-антител к предранним антигенам *HSV-1,2* и раннему антигену *EBV* (маркеров реактивации HH*V*). Концентрацию IL-1β, IFNγ, MCP-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12p70, IL-13, IL-18, TNFα, GM-CSF, Eotaxin, GRO-α, IP-10, MIP-1α, MIP-1β, SDF-1α, RANTES определяли в мультиплексном анализе, TGF-β1, TGF-β2 – в иммуноферментном анализе. В зависимости от наличия и активности увеита выделили 3 группы пациентов с ББ: 1-я группа – активный увеит, 2-я группа – увеит в ремиссии, 3-я группа – ББ без поражения глаз. По результатам серологического анализа в каждой группе выделили 2 подгруппы: а) пациенты с наличием антител-маркеров реактивации хотя бы одного из исследованных *HHV*, б) пациенты, хронически инфицированные *HHV*, без признаков реактивации. Средний уровень и частоту выявления цитокинов и хемокинов у пациентов с активными увеитами (1а, 1б) и в стадии ремиссии (2а, 2б) сравнивали с результатами обследования пациентов без поражения глаз (3а, 3б), сопоставляли подгруппы с хронической ВГЧ-инфекцией (подгруппа «б») и ее реактивацией (подгруппа «а»).

Достоверное повышение сывороточного содержания хемокинов MCP-1/CCL2, MIP-1α/CCL3, MIP-1β/CCL4, RANTES/CCL5), IP-10, SDF-1α, а также IFNγ, TGF-β1 и TGF-β2 отмечено у пациентов с увеитами (независимо от их активности) и маркерами реактивации *HHV* по сравнению с пациентами без увеитов.

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Полученные данные указывают на возможное влияние реактивации хронических герпесвирусных инфекций на системную продукцию цитокинов и хемокинов у пациентов с ББ и увеитами, причем наибольшие изменения касаются хемокинов.

Ключевые слова: болезнь Бехчета, вирусы герпеса человека, цитокины, хемокины, увеит, реактивация ВГЧ

EFFECT OF HUMAN HERPES VIRUS REACTIVATION ON SYSTEMIC CYTOKINE PRODUCTION IN PATIENTS WITH BEHCET'S DISEASE AND UVEITIS

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Abstract. Behcet's disease (BD) is a systemic autoinflammatory-autoimmune disease (chronic systemic vasculitis) of unknown etiology, almost 70% of patients develop uveitis. BD pathogenesis is complex, human herpesviruses (*HHV*) play an important role among infectious trigger factors. Ability of herpesviruses to modulate cytokine production and evade host's immune response is known. Aim of the study was to assess the effect of *Herpes simplex virus type 1*, *Herpes simplex virus type 2*, *Cytomegalovirus*, *Epstein-Barr virus* on systemic levels of chemokines, pro- and anti-inflammatory cytokines in BD with and without uveitis. Serum samples were collected from 116 BD patients chronically infected with HHV and examined in ELISA-test for markers of HHV reactivation (IgG-antibodies to immediate early HSV antigens 1, 2 and CMV, early EBV antigen). Concentration of IL-1β, IFNγ, MCP-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12p70, IL-13, IL-18, TNFα, GM-CSF, Eotaxin, GRO-α, IP-10, MIP-1α, MIP-1β, SDF-1α, RANTES detected in multiplex analysis. TGF-β1, TGF-β2 were measured in ELISA-test. Depending on presence and activity of uveitis 3 groups of patients with BD were identified: group 1 – active uveitis, group 2 – remission of uveitis, group 3 – BD without ocular manifestations. After serological study 2 subgroups were highlighted in each group: a) patients with antibody markers of reactivation of at least one HHV, b) patients chronically infected with HHV, without serological signs of reactivation. Mean level and detection rate of cytokines and chemokines in patients with active uveitis (1a, 1b) and in remission (2a, 2b) were compared with patients without eye damage (3a, 3b). Chronic HHV infection (subgroup "b") was compared with reactivation (subgroup "a"). A significant increase of MCP-1/CCL2, MIP-1α/CCL3, MIP-1β/CCL4, RANTES/CCL5, IP-10, SDF-1α chemokines in serum, as well as IFNγ, TGF-β1, and TGF-β2 was observed in patients with uveitis (regardless of their activity) and HHV reactivation compared to patients without uveitis. Our data indicate that systemic production of cytokines and chemokines in BD patients and uveitis could be affected by the activity of chronic herpesvirus infections, and the greatest changes are related to chemokines.

Keywords: Behcet's disease, human herpes viruses, cytokines, hemokines, uveitis, HHV reactivation

Introduction

Behcet's disease (BD) is a systemic autoinflammatory-autoimmune disorder (chronic systemic vasculitis) of unknown etiology characterized by recurrent inflammatory lesions in various organs [12]. Inflammation of the vascular tract of the eye (uveitis) mainly involves posterior segment and is considered to be one of the most common symptoms in BD [3].

BD pathogenesis is multilayered and largely unclear. It is believed that hyperactivation of innate and adaptive immunity can be triggered by infectious factors, particularly herpes viruses, which then cause production of a large number of cytokines and chemokines aimed at suppressing the pathogen life cycle [4, 10, 13]. An experimental *HSV*-induced BD model was developed in mice [10].

Human herpes viruses (*Human herpesvirida*, *HHV*) hold a pivotal place in the structure of infectious and infection-associated eye pathology, being not only etiological agents but also factors that trigger and aggravate the inflammatory process. It is accounted

for by their wide distribution in human population, lifelong persistence in infected host and tendency to reactivation, which often leads to manifestation of a new infection or exacerbation of existing disease. Persistent nature of *HHV* infections is associated with their ability to evade host immune system by modulating systemic and local cytokine production.

The aim of this study was to assess an effect of some reactivated *HHVs*: *Herpes simplex virus type 1, HSV-1*, *Herpes simplex virus type 2, HSV-2*, *Cytomegalovirus, CMV*, *Epstein-Barr virus, EBV*, on systemic level of chemokines, pro- and anti-inflammatory cytokines in BD with and without uveitis.

Materials and methods

Serum samples were collected from 116 chronically *HHV*-infected BD patients. Mean age ranged from 19 to 61 (mean age 36,6±9,9) years, in 73 males and 43 females.

BD was diagnosed at the V.A. Nasonova Research Institute of Rheumatology in accordance with the International Criteria for Behcet's Disease (ICBD, 2014) [5]. Ophthalmological examination was performed at the Helmholtz National Medical Research Center of Eye Diseases.

During initial visit to ophthalmologist blood sample from cubital vein was collected. IgM- and IgG-antibodies against *HSV-1, HSV-2, CMV, EBV* structural late antigens (test systems VectoHSV-IgM, VectoHSV-1,2-IgG; VectoCMV-IgM, VectoCMV-IgG; VectoEBV-VCA-IgM, VectoEBV-NA-IgG, AO Vector-Best, Russia) were measured by using ELISA assay. Reactivation of chronic *HHV* infection was diagnosed by detecting specific IgG antibodies to nonstructural immediate-early antigens of *HSV-1, HSV-2, CMV* (test systems BioSet-aktiv-HSV, BioSet-aktiv-CMV, Bioservice Biotechnology Company Ltd, Moscow) and early antigens of *EBV* (test system VectoEBV-EA-IgG, AO Vector-Best, Russia) in serum samples [8].

Serum levels of IL-1β, IFNγ, MCP-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12p70, IL-13, IL-18, TNFα, GM-CSF, Eotaxin, GRO-α, IP-10, MIP-1α, MIP-1β, SDF-1α, RANTES were detected using the Procarta PlexTM test system "Human Th1/Th2 & Chemokine 1 Panel 20 plex" (eBioscience, Austria) on a MAGPIX analyzer (Luminex Corp., USA) [11]. TGF-β1, TGF-β2 cytokines were measured in ELISA-test (Invitrogen test systems, Thermo Fisher Scientific, Austria).

Statistical analysis was performed by using the STATISTICA 12.0 software. The data were processed by using Fisher's exact test and Student's T-test. Differences were considered significant at $p \leq 0.05$.

Results and discussion

116 BD patients were divided into 3 groups depending on verified uveitis and its activity: group 1 – active uveitis (n = 41); group 2 – remission of uveitis (n = 64); group 3 – BD without ocular manifestations (n = 11). In each group 2 subgroups were highlighted: a-patients with serological markers of reactivated chronic *HHV* infection, b-patients without serological markers of reactivated chronic *HHV* infection.

Reactivation of at least one herpes virus was detected in 50-58% of BD patients; albeit, these data did not significantly differ from those in subjects with endogenous uveitis of other etiology ($p > 0.05$).

Mean level and detection rate of cytokines and chemokines in patients with active uveitis (1a, 1b) and in remission state (2a, 2b) were compared with patients without eye involvement (3a, 3b), and inter-subgroup comparison was performed for patients with chronic *HHV* infection (subgroup "b" *vs* subgroup "a") (Table 1).

Because uveitis is one of the most common symptoms of BD, group 3 contained very few patients. Therefore, the quantitative data obtained for several cytokines and chemokines are insufficient for analysis, and requires to be further investigated (Table 1).

Changes in the systemic production of cytokines and chemokines in BD patients with uveitis associated with reactivation of chronic HHV infection.

Differences in systemic immune mediator production were more significant in patients with uveitis having serological markers of *HHV* reactivation, both with active uveitis (group 1a) and in remission phase (group 2a), when compared to patients without eye involvement (group 3). Levels of several immune mediators, mainly chemokines, were significantly increased, and detection rate of investigated cytokines changed much less frequently (Table 2).

Chemokines ensure increased influx of cells into site of inflammation. MCP-1, MIP-1α, MIP-1β, RANTES (CC-chemokines) induce chemotaxis of monocytes, T-lymphocytes, NK-cells, dendritic and other cells to the site of inflammation [1, 3, 4]. Both active uveitis and uveitis in remission phase are featured with increased systemic production of CCL-chemokines (MCP-1/CCL2, MIP-1α/CCL3, MIP-1β/CCL4, RANTES/CCL-5) and CXCL-chemokines (IP-10, SDF-1α), as well as IFNγ, TGF-β1 and TGF-β2.

Histological findings in BD are characterized by non-granulomatous occlusive vasculitis with chronic perivascular infiltration by neutrophils and T-lymphocytes [3]. CXCL12 chemokine family includes angiostatic IP-10 chemokine and SDF-1α – a chemoattractant for B-lymphocytes. According to

TABLE 1. SERUM LEVELS OF CYTOKINES (pg/ml) IN BD PATIENTS WITH AND WITHOUT UVEITIS IN CONDITIONS OF CHRONIC HHV INFECTION AND ITS REACTIVATION

Cytokines	Serum levels (pg/ml) and detection rate (%)					
	Group 1 BD with active uveitis (n = 41)		Group 2 BD with remission of uveitis (n = 64)		Group 3 BD without uveitis (n = 11)	
	1a reactivation of chronic HHV infection (n = 24)	1b chronic HHV infection (n = 17)	2a reactivation of chronic HHV infection (n = 40)	2b chronic HHV infection (n = 24)	3a reactivation of chronic HHV infection (n = 6)	3b chronic HHV infection (n = 5)
IFNγ	5.5±0.7* p^{1a-3a} = 0.042 14.75%** p^{1a-2a} = 0.048#	3.8±0.4 9-53%	7.0±0.8 p^{2a-3a} = 0.001 24.60%	4.9±1.0 18.24%	3.8±0.3 3.50%	3.3±0.5 2.40%
MCP-1	87.0±9.8 p^{1a-3a} = 0.002 24.100%	62.7±13.7 17.100%	99.3±21.4 p^{2a-3a} = 0.016 40.100%	91.5±15.1 p^{2b-3b} = 0.001 24.100%	38.3±10.5 6.100%	32.2±4.6 5.100%
IL-8	5.6±1.1 6.25%	6.7±5.8 2.12%	9.4±5.9 6.15%	31.4±16.3 7.29%	0	2.42 1.20%
IL-18	7.6±1.3 p^{1a-2a} = 0.02 17.71%	12.2±4.4 11.65%	16.3±3.4 p^{2a-3a} = 0.040 25.66%	13.0±4.3 19.79%	7.7±2.1 6.100%	4.1±3.4 3.60%
IL-1β	1.40±0.13 p^{1a-2a} = 0.037 4.16.7%	9.8±6.5 2.12%	1.0±0.1 8.20%	1.4±0.3 7.29%	0	5.7 1.20%
IL-12p70	3.40±0.15 12.50%	3.7±0.4 5.29%	4.9±1.6 18.45%	3.4±0.2 14.58%	0	2.8 1.20%
IL-2	16.0±8.8 5.21%	13.9±4.3 5.29%	9.9±4.7 4.10% p^{2a-2b} = 0.023	7.7±2.2 8.33%	12.5 1.17%	21 1.20%
IL-4	10.5±3.5 6.25%	17.6±12.0 2.12%	6.9±0.3 12.30%	9.0±2.4 10.41%	0	5.7 1.20%
IL-5	0 0	14.7 1.6%	0 0	0 0	0	11.8 1.20%
IL-6	9.9±3.1 p^{1a-2a} = 0.008 6.25%	24.7±1.5 p^{1b-2b} = 0.037 2.12%	5.9±2.2 12.30%	9.9±2.6 9.38%	12.5 1.17%	0
TNFα	2.4±0.4 10.42%	4.2±1.8 3.18%	2.1±0.3 14.35%	3.7±0.9 12.50%	0.1 1.17%	10.4±9.0 2.40%
GM-CSF	24.3±4.8 3.13%	20.6±14.4 2.12%	14.4±1.8 2.5%	22.1±4.5 4.17%	0	0
Eotaxin	57.3±7.6 24.100%	65.2±12.6 17.100%	71.1±6.2 p^{2a-3a} = 0.016 40.100%	61.8±7.9 24.100%	43.1±9.3 6.100%	42.0±9.7 5.100%
GRO-α	27.5±14.6 12.50%	30.8±21 13.77%	12.3±2.5 p^{2a-3a} = 0.029 21.53%	39.5±17.4 11.46%	6.4±0.4 3.50%	8.9±2.9 2.40%
IP-10	38.7±11.0 p^{1a-3a} = 0.006 24.100%	70.3±43.0 17.100%	35.9±6.2 p^{2a-3a} = 0.0008 40.100%	43.3±14.9 p^{2b-3b} = 0.048 24.100%	12.8±1.6 6.100%	12.1±2.1 5.100%
MIP-1α	13.0±3.6 p^{1a-3a} = 0.016 15.63%	11.0±2.2 14.88%	9.1±1.5 p^{2a-3a} = 0.0001 27.68%	18.7±4.9 13.54%	1.7±0.6 3.50%	3.86 1.20%

Cytokines	Serum levels (pg/ml) and detection rate (%)					
	Group 1 BD with active uveitis (n = 41)		Group 2 BD with remission of uveitis (n = 64)		Group 3 BD without uveitis (n = 11)	
	1a reactivation of chronic HHV infection (n = 24)	1b chronic HHV infection (n = 17)	2a reactivation of chronic HHV infection (n = 40)	2b chronic HHV infection (n = 24)	3a reactivation of chronic HHV infection (n = 6)	3b chronic HHV infection (n = 5)
MIP-1β	98±16 p^{1a-3a} = 0.002 23.96%	69.0±19.5 17.100%	84.2±11.5 p^{2a-3a} = 0.002 39.98%	116.1±23.2 p^{2b-3b} = 0.025 23.96%	36.5±8.7 6.100%	48.9±16.2 5.100%
SDF-1α	436±27 p^{1a-3a} = 0.0009 24.100%	418±28 $p^{1б-3б}$ = 0.02 17.100%	444.5±24.2 p^{2a-3a} = 0.0001 40.100%	525.5±57.3 p^{2b-3b} = 0.003 24.100%	302.6±23.2 6.100%	300.0±37.3 5.100%
IL-13	2.2±0.8 11.46%	2.8±1.7 4.24%	2.3±1.4 15.38%	1.2±0.2 10.42%	1.8 1.17%	2.3±1.9 2.40%
RANTES	64.6±7.4 p^{1a-3a} = 0.0015 24.100%	56.5±7.0 17.100%	73.0±6.6 p^{2a-3a} <0.0001 40.100%	72.8±8.7 24.100%	37.5±2.1 6.100%	56.9±14.1 5.100%
TGF-β1	29753±3919 p^{1a-3a} = 0.002 21.100%	25774±4095 20.100%	26993±2312 p^{2a-3a} = 0.0002 34.100%	22967±3484 24.100%	14561±2019 8.100%	29296±7510 4.100%
TGF-β2	6700±1354 p^{1a-3a} = 0.002 20.100%	3485±630 18.100%	5568±697 p^{2a-3a} = 0.0003 38.95%	4525±664 23.100%	1417±767 2.66%	2552±2480 3.75%

Note. * 5.5±0.07, mean serum cytokine concentration, pg/ml (M±m); ** 14.75%, cytokine detection rate: absolute count and detection percentage; # p^{1a-2a} = 0.048, statistical significance between two comparison groups P value of 0.05 or less was considered as statistically significant.

TABLE 2. DIRECTION OF CHANGES IN SERUM LEVELS OF CYTOKINES AND CHEMOKINES IN PATIENTS WITH ACTIVE UVEITIS AND IN REMISSION PHASE IN COMPARISON WITH BD PATIENTS WITHOUT EYE INVOLVEMENT IN CONDITIONS OF CHRONIC HHV INFECTION AND ITS REACTIVATION

Serum levels of cytokines	Reactivation of chronic HHV infection		Chronic HHV infection	
	1a active uveitis	2a remission of uveitis	1b active uveitis	2b remission of uveitis
Increased*	IFNγ	IFNγ	SDF-α/CXCL12	MCP-1/CCL2
	MCP-1/CCL2	MCP-1/CCL2		IP-10/CXCL10
	MIP-1α/CCL3	MIP-1α/CCL3		MIP-1β/CCL4
	MIP-1β/CCL4	MIP-1β/CCL4		SDF-1α/CXCL12
	RANTES/CCL5	RANTES/CCL5		
	IP-10/CXCL10	IP-10/CXCL10		
	SDF-1α/CXCL12	SDF-1α/CXCL12		
	TGF-β1	TGF-β1		
	TGF-β2	TGF-β2		
		GRO-α/CXCL1		
		Eotaxin/CCL11		
		IL-18		
Decreased				

Note. * p < 0.05

some reports, IP-10 is involved in the pathogenesis affecting nervous system in BD [6]. Thus, its role in the pathogenesis of peripheral portion of the visual analyzer – retina, cannot be ruled out.

During reactivation of chronic *HHV* infection, levels of IFNγ significantly increased in serum of patients with BD and uveitis, regardless of the activity of intraocular inflammation (groups 1a, 2a), when compared with patients without uveitis (group 3a). Increase of serum IFNγ level in patients with active uveitis associated with BD was reported by Zhu Y. et al. [14]. Authors discussed a role of infections as a factor stimulating T-lymphocytes to intensively secrete several cytokines, although they did not perform such analysis. We believe that increased levels of serum IFNγ in patients with serological markers of reactivated chronic *HHV* infection is necessary to suppress viral replication. Clinical remission of uveitis cannot completely exclude subclinical activity of intraocular inflammation, which is often supported by long-term replication of herpes viruses.

A significant increase of TGF-β1 and TGF-β2 serum levels in patients with active and inactive uveitis was observed only in association with *HHV* reactivation. TGF-β is a pleiotropic context-dependent cytokine which can induce development of Th17 or Treg-cells [76].

In remission of uveitis (group 2a) we detected an increased level of the two other angiogenic chemokines: Eotaxin and GRO-α, as well as immunoregulatory IL-18 cytokine, which induces IFNγ production, thus determining its important role in the host anti-infectious defense [2].

Belguendous H. et al. [2] found a significant increase of serum IL-18 in patients with active *vs* inactive uveitis. Corticosteroid therapy reduced IL-18 levels and decreased disease activity. It was considered that IL-18 might serve a good marker for monitoring activity of uveitis and related treatment efficacy. However, in our study patients with active uveitis and HHV reactivation had significantly higher serum IL-18 level than patients with remission of uveitis. This might result from intensive corticosteroid treatment during the period of active uveitis.

Systemic production of cytokines and chemokines in BD with uveitis coupled to chronic *HHV* without reactivation differed from patients without eye involvement by showing fewer range of produced immune mediators: systemic level of SDF-α was significantly higher both in active uveitis and in remission stage, than in patients without uveitis. Patients with remission of uveitis also showed significant increase in 2 other immune mediators: IP-10 and MIP-1β. Serum SDF-α turned out to be the only chemokine which was significantly elevated in all examined BD subgroups with uveitis than in the corresponding subgroups without eye involvement. SDF-α has been shown to be crucially involved in both physiological and pathological processes [9].

In contrast to BD without uveitis, patients with remission of uveitis produced a wider range of immune mediators than those with active uveitis, which is hard to interpret precisely but their protective role by lowering the risk of ocular inflammation relapse with underlying subclinical herpes viruses replication, cannot be ruled out.

It is noteworthy that all patients with uveitis showed increased concentration of GRO-α chemokine compared to patients without uveitis. Besides its oncogenic properties, GRO-α is a pro-angiogenic chemokine and plays an important role in inflammation and wound healing.

Thus, our data indicate that the systemic production of cytokines and chemokines in BD patients with uveitis is affected by the activity of chronic herpesvirus infections, and the most prominent changes are related to chemokines.

References

1. Abu El-Asrar A.M., Berghmans N., Al-Obeidan S.A., Gikandi P.W., Opdenakker G., van Damme J., Struyf S. The CC chemokines CCL8, CCL13 and CCL20 are local inflammatory biomarkers of HLA-B27-associated uveitis. *Acta Ophthalmol., 2019, Vol. 97, no. 1, pp. e122-e128.*

2. Belguendous H.,Messaoudene D., Lahmar-Belguendouz K., Djeraba Z., Otmani F., Terahi M., Tiar M., Hartani D., Lahlou-Boukoffa O.S., Touil-Boukoffa C. *In vivo* and *in vitro* IL-18 production during uveitis associated with Behçet disease: effect of glucocorticoid therapy. *J. Fr. Ophtalmol., 2015, Vol. 38, no. 3, pp. 206-212.*

3. Ksiaa I., Abroug N., Kechida M., Zina S., Jelliti B., Khochtali S., Attia S., Khairallah M. Eye and Behçet's disease. *J. Fr. Ophtalmol., 2019, Vol. 42, no. 4, pp. e133-e146.*

4. Leccese P., Alpsoy E. Behçet's disease: an overview of etiopathogenesis. *Front. Immunol., 2019, Vol. 10, 1067.* doi: 10.3389/fimmu.2019.01067.

5. Lisitsyna T.A., Alekberova Z.S., Goloeva R.G., Davydova G.A. Behcet's disease: clinical manifestations, current principles of diagnosis and therapy. *Rheumatology Science and Practice, 2019, Vol. 57, no. 5, pp. 553-563.* (In Russ.)

6. Mesquida M., Molins B., Llorenç V., Sainz de la Maza M., Hernandez M.V., Espinosa G., Adán A. Proinflammatory cytokines and C-reactive protein in uveitis associated with Behçet's disease. *Mediators Inflamm., 2014, Vol. 2014, 396204.* doi: 10.1155/2014/396204.

7. Moskalev A.V., Rudoy A.S., Apchel A.V., Zueva V.O., Kazimova O.E. Features of biology of transforming growth factor β and immunopathology. *Bulletin of Russian Military Medical Academy, 2016, Vol. 2, no. 54, pp. 206-216.* (In Russ.)

8. Petrovskaya M.S., Krichevskaya G.I., Denisova E.V., Katargina L.A., Kulikova I.G. Importance of Epstein–Barr virus infection in pathogenesis of proliferative complications in children with endogenous uveitis. *Russian Journal of Infection and Immunity*, *2019, Vol. 9, no. 5-6, pp. 800-804*. (In Russ.) doi: 10.15789/2220-7619-2019-5-6-800-804.

9. Prokhorova O.V., Olina A.A., Tolibova G.Kh., Tral' T.G. Stromal cell-derived factor: pathological and clinical potentialities. *Russian Journal of Woman and Child Health, 2020, Vol. 3, no. 3, pp. 198-204.* (In Russ.)

10. Sayeed H.M., Lee E.S., Byun H.O., Sohn S. The role of CCR1 and therapeutic effects of anti-CCL3 antibody in herpes simplex virus-induced Behçet's disease mouse model. *Immunology, 2019, Vol. 158, no. 3, pp. 206-218.*

11. Sorozhkina E.S., Balatskaya N.V., Davidova G.I., Lisitsyna T.A. Cytokine screen in serum of BD patients with eye lesions. *Medical Immunology (Russia), 2017, Vol. 19, Special edition, p. 225.* (In Russ.)

12. Tong B., Liu X., Xiao J., Su G. Immunopathogenesis of Behcet's Disease. *Front. Immunol., 2019, Vol. 10, 665*. doi: 10.3389/fimmu.2019.00665.

13. Zhou Z.Y., Chen S.L., Shen N., Lu Y. Cytokines and Behcet's disease. *Autoimmun. Rev., 2012 ,Vol. 11, no. 10, pp. 699-704.*

14. Zhu Y., Qiu, Y., Yu H., Yi S., Su W., Kijlstra A., Yang P. Aberrant DNA methylation of GATA binding protein 3 (GATA3), interleukin-4 (IL-4), and transforming growth factor-β (TGF-β) promoters in Behcet's disease. *Oncotarget*, *2017, Vol. 8, no. 38, pp. 64263-64272.*

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