Epidemiology and Therapy of Chronic Herpes Virus Infection with Genital Herpes Manifestations

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Anaferon-supplemented complex therapy of chronic recurrent genital herpes reduced clinical symptoms of the disease and normalized the content of immunocompetent cells. Changes in the level of immunocompetent cells depended on the severity of genital herpes.

Key Words: *chronic recurrent herpes-virus infection; cytokines; anaferon*

Therapy of chronic herpes-virus infection with localization of the process in the genital area is still a problem for physicians of different specializations [2,4,8]. In Russia, chronic recurrent genital herpes (CRGH) is not a subject to official registration [6]. According to reports of the Research Center of Obstetrics, Gynecology, and Perinatology, Federal Agency of Medical Technologies, in 1992 the incidence of herpes simplex infections of genitals in women in Moscow was 19.2% [3]. The number of patients with CRGH per 100,000 population is within 1% of sexually transmitted infections [7]. The number of patients with newly acquired genital herpes increases by more than 10% per year. There are data, that 15% population in Russia have CRGH, the relapses are noted in 50-75% cases [1]. According to reports of Dermatovenereological Service, Ministry of Health of Samara Region, the percent of patients with herpetic infection of urogenital organs among sexually transmitted diseases (per 100,000 population) varied from 0.6 to 38.6% in various population centers over 5 years (Table 1).

Higher incidence of the disease is noted in urban population (7.2-19.9%) compared to this parameter in rural population (2.4-4.3%). Over 5 years (1998-2002), the incidence of CRGH in urban population of the Samara region increased by 53.47%, whereas in rural area this rise during the corresponding period was 0.94%.

These low values of the incidence of herpetic infection (including genital herpes) can be explained by incomplete registration of the disease by attending physicians.

Here we evaluated immunological parameters in patients with CRGH in rural and urban populations.

MATERIALS AND METHODS

The study included 209 individuals aging 22-45 years (Table 2). The main group (n=99) comprised patients with CRGH (41 men and 58 women, history of the disease 5.00±2.13 years). The control group consisted of somatically healthy donors (n=110, Table 3) without clinical signs of herpetic infection (lesions on the skin and/or mucosa of any localization). According to the results of cluster analysis, patients of the main group were divided into 3 subgroups with mild, moderate, and severe forms of the disease.

Complex therapy of CRGH included antiviral drugs in combination with immunocorrectors and local preparations (Table 4). The treatment was prescribed during exacerbation (stage I) and was continued in the period between relapses (stages II and III). The duration of stage I was 10 days for patients with mild form and 20 days for patients with moderate and severe forms of the disease. The duration of stages II and III was 1 month in all groups. The stages of therapy in all patients followed successively with a maximum interval of 7 days.

Clinical and laboratory examination was performed before and 3 months after the start of staged complex therapy. In all examinees, the expression of membrane

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TABLE 1. Incidence of CRGH in Population of Samara Region (%)

Territory		1998	1999	2000	2001	2002	Dynamics
Cities and towns	Samara	6.7	6.7	7.3	11.4	19.0	66.29
	Tol'yati	7.6	19.5	26.6	16.7	27.8	67.03
	Novokuibyshevsk	5.9	7.7	4.3	5.1	9.4	84.38
	Chapaevsk	9.6	15.6	14.6	8.6	17.3	102.22
	Otradnyi	13.0	7.4	7.5	24.3	26.4	8.48
	Zhigulevsk	21.4	24.6	31.0	27.9	24.5	-11.96
	Oktyabr'sk		9.6	9.6	38.6	3.2	-91.60
Districts	Kinel'skii	2.5		1.2	1.2	6.2	414.05
	Krasnoyarskii	3.8	5.6	7.4	9.3	11.3	21.03
	Pokhvistnevskii		3.3		3.3	10.2	206.65
	Privolzhskii	19.7	7.9	3.9	7.8	7.9	0.77
	Sergievskii	2.0	4.0	2.0	2.0	2.1	3.94
	Koshkinskii			7.7	11.6	3.8	-66.84
	Chelno-Vershinskii		14.3		9.8	4.9	-49.69
Averaged data							
Urban area		7.2	11.1	13.4	13.0	19.9	53.47
Rural area		2.4	3.6	2.1	4.2	4.3	0.94
Region		5.9	9.1	10.5	10.7	15.9	48.32

TABLE 2. Distribution of Examinees by the Place of Residence

Residence	Control group	CRGH
Urban	68	56
Rural	42	43
Total	110	99

antigens $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD22^+$, $CD25^+$, and HLA-DR on peripheral blood lymphocytes (immunogram) was analyzed using FITC-labeled monoclonal antibodies IKO 90, 31, 86, 180, 15, 116, and 1, respectively (BioMedSpektr) and EPICS XL laser flow cytofluorometer (Coulter). Activity of complement was evaluated by titration by 50% hemolysis of sheep erythrocytes and expressed as CH_{50}. Activity of complement components C1, C2, C3, C4, and C5 was measured by hemolytic titration using commercial kits (Biomed Research-and-Production Company). The content of circulating immune complexes was determined by precipitation with polyethyleneglycol PEG-6000 (Indiktor Company). The content of IgE to herpes simplex virus and cytomegalovirus was analyzed by IEA (Vektor-Best). The levels of IL-4, IFN-α, IFN-γ, and TNF-α were determined by IEA (Vektor-Best). IL-2 in blood serum was quantitatively assayed by ELISA (Proteinovyi Kontur).

The samples were compared using methods of variation statistics (Student tests) and nonparametric

TABLE 3. Age and Gender Distribution of Examinees

Sex	Control group			CRGH		
	22-30 years	31-40 years	41-45 years	22-30 years	31-40 years	41-45 years
Men	18	16	14	14	12	9
Women	23	22	17	30	20	14
Total	41	38	31	44	32	23

TABLE 4. Drugs Used in Therapy of CRGH

Stage of therapy	Severity of CRGH		
	mild	moderate	severe
I	1. Famvir, 250 mg 3 times a day for 7 days	1. Famvir, 250 mg 3 times a day for 7 days	1. Famvir, 250 mg 3 times a day for 7 days
	2. Neovir, 2 ml/day i/m every other day, 5 injections	2. Neovir, 2 ml/day i/m every other day, 5 injections	2. Neovir, 2 ml/day i/m every other day, 5 injections
	3. ViruMerz serol, 3 times a day locally for 5 days	3. Polyoxidonium, 6 mg/day i/m every other day, 10 injections	3. Polyoxidonium, 6 mg/day i/m every other day, 10 injections
		4. ViruMerz serol, 5 times a day locally for 5 days	4. ViruMerz serol, 5 times a day locally for 5 days
II	1. Alpizarin, 2 tablets 2 times a day for 10 days	1. Alpizarin, 2 tablets 2 times a day for 10 days Repeated course after 10 days	1. Alpizarin, 2 tablets 2 times a day for 14 days. Repeated course after 10 days
	2. Centrum, 1 tablet a day for 1 month	2. Cycloferon, 2 ml/day i/m, 10 injections	2. Cycloferon, 2 ml/day i/m, 10 injections
		3. Centrum, 1 tablet a day for 1 month	3. Centrum, 1 tablet a day for 1 month
III	Anaferon, 1 tablet a day for 1 month	Anaferon, 1 tablet a day for 1 month	Anaferon, 1 tablet a day for 1 month

Note. i/m: intramuscularly.

Mann—Whitney test. The shape of distribution and differences of the empirical distribution from normal distribution were evaluated using Kolmogorov—Smirnov and χ^2 tests. Cluster analysis was used for distribution of patients into groups with different severity of the disease.

TABLE 5. Changes in Local Manifestations of CRGH under the Effect of Complex Therapy

Clinical sign	Severity of the disease	Before treatment		After treatment	
		M±*SE*	incidence, %	*M*±*SE*	incidence, %
Number of localizations, score	Mild	0.62±0.14	38.9	0.45±0.16	85.9
	Moderate	1.06±0.04	36.7	0.91±0.045*	8.2
	Severe	2.06±0.04	24.4	1.25±0.09**	5.9
Area, cm	Mild	0.77±0.29	7.8	0.45±0.16	46.6
	Moderate	2.45±0.08	32.7	1.45±0.10**	46.7
	Severe	2.97±0.03	59.5	1.94±0.12**	6.7
Course	Mild	0.88±0.12	7.7	0.63±0.11	13.3
	Moderate	1.0±0.001	63.3	0.91±0.04	76.7
	Severe	1.0±0.001	29	1.0±0.01	10.4
Incidence of attacks	Mild	0.627±0.14	14.1	0.45±0.16	16.1
	Moderate	2.45±0.09	30.0	1.45±0.11**	38.2
	Severe	2.66±0.11	56.7	1.75±0.13**	45.7
Duration of exacerbation, days	Mild	6.62±1.62	6.7	4.0±1.43*	19.1
	Moderate	15.09±1.58	40.0	10.89±0.82**	79.4
	Severe	15.41±0.65	53.3	13.34±0.83**	1.5

Note. *p<0.05, **p<0.001 compared to clinical symptoms before therapy. Abortive forms of skin lesions were scored as 0.5.

TABLE 6. Blood Levels of Circulating Immune Complexes and Activity of Complement Components in Patients with CRGH before Therapy (*M*±*m*)

Parameter		Form of the disease		
		mild	moderate	severe
Circulating immune complexes, %		53.43±6.12**	61.56±2.15*	62.86±5.37*
Hemolytic activity of complement, % of hemolysis	C50	57.29±5.42	49.06±1.73	45.50±4.35
	C1	26.43±6.34	30.32±1.71	29.38±3.38
	C2	15.00±1.89	20.35±1.28	17.69±2.61
	C3	22.8±3.76	25.12±1.48	21.25±2.98
	C4	24.29±3.17	27.82±1.62	20.94±3.10
	C5	27.14±2.64	26.89±1.37	20.31±3.11

Note. *$p<0.01$, **$p<0.001$ compared to healthy donors (83.71±2.39%).

RESULTS

Alleviation of clinical symptoms of CRGH was noted after treatment (Table 5).

No significant differences between the rural and urban populations by the expression of membrane antigens were revealed. The level of circulating immune complexes was significantly increased in patients of the main group compared to the control (Table 6).

Analysis of cytokine content in CRGH patients from rural and urban populations revealed the following relationships: IL-4 content was elevated in 61.3% individuals from the urban population, while in 100% rural residents all parameters were within the normal range. The content of IFN-α was elevated in 37.5% urban residents, while in 100% rural residents this parameter was within the normal range.

Analysis of the dynamics of cell parameters of the immunogram before and after complex staged therapy showed a modulating mechanism of drug action: they not only produced a stimulating effect (increased the levels of lymphocyte populations), but also normalized the ratio of immunocompetent cells often reducing elevated parameters. The higher was the initial level of $CD3^+$ lymphocytes, the less pronounced was its change. It should be noted that the level of $CD3^+$ increased after treatment in patients with initial $CD3^+$ content <50%. remained unchanged in patients with initial $CD3^+$ content 50-65%, and decreased in patients with initial $CD3^+$ content >65%.

Thus, we demonstrated a modulating effect of complex staged therapy: decrease in elevated and increase in lowered values of $CD3^+$. This relationship can be described by a linear regression equation $CD3^+_2$-$CD3^+_1$=40.4-0.62 and proves the modulating effect of therapy.

Similar relationship was observed for the content of $CD4^+$ and $CD8^+$ lymphocytes.

Cluster analysis of changes in the cellular component depending on the severity of the disease under the effect of therapy revealed the following relationships. In patients with mild CRGH, the content of $CD3^+$ and $CD8^+$ lymphocytes increased ($p<0.01$). In patients with moderate CRGH, the content of $CD3^+$ and $CD4^+$ lymphocytes increased ($p<0.01$). In patients with severe CRGH, the content of $CD8^+$ ($p<0.05$), $CD3^+$ ($p<0.01$) and $CD4^+$ lymphocytes ($p<0.001$) increased.

During complex therapy, no side effects and no cases of bad tolerance of the preparations were noted.

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