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UROGENITAL PATHOLOGY, HERPETIC INFECTION AND THE STATE OF IMMUNITY

M. V. Novikov, V. S. Goydyk

SE "Ukrainian Research Institute for Medicine of Transport", Odessa, Ukraine

Abstract

The main indexes of immune status have been learnt in 150 patients with urogenital infection. The results obtained were compared with those of 30 healthy volonteers. The disturbanses of immunity and formation of the secondary immunodeficiency in the group of patients with virus damage of urogenital system had been revealed. To correct timely therapeutic schemes and increase the treatment's efficacy additional researches are necessary.

Key words: urogenital pathology; herpetic infection; cytomegalovirus; immunity; immunodeficiency.

Urgency. Since viral infections have taken a prominent place in the etiology of infectious diseases, replacing bacterial infections, the group of herpesviruses has constantly attracted the attention of researchers and clinicians. This is due to a number of factors. First, herpesviruses are one of the most numerous families. To date, more than 100 of its representatives have been identified and classified - etiological factors of human diseases, wild and domestic animals, amphibians and reptiles. Eight antigenic serotypes were isolated directly from humans. The herpetic etiology of the disease was first confirmed more than a hundred years ago, when in 1912 W. Grütter found viral inclusions in a patient with herpetic keratitis [1]. Due to the variety of routes of infection and target organs, the herpesvirus

etiology has a large (about 40 nosologies) and heterogeneous group of diseases, including the proven role of herpesviruses in the induction of tumor processes.

Second, the vast majority of diseases caused by herpesviruses are chronic. According to WHO, 70 - 90 % of the world's population is infected with one or more viruses of this family, and most carry the virus for life [2, 3].

Directly "herpes infection" is a disease caused by herpes simplex virus (HSV, HSV) type 1 and 2. Annual recurrences of herpes infection have from 12 to 25% of those infected, and another 30% - latent form of the disease. The presence of immunodeficiency increases the frequency of relapses (including pregnancy, HIV infection, oncopathology, manifestations of intercurrent infections, excessive insolation, stressful situations, hormonal disorders) [4]. There is evidence that from 8 to 15% of patients with herpes type 1 and 2 have immunodeficiency of varying degrees [5, 6]. A number of studies have shown that the rapid increase in herpes infection preceded a significant increase in new cases of HIV infection [7].

A separate problem, which has become widespread, is herpetic lesions of the urogenital sphere. The urgency of the problem follows from the above characteristics of the family *Herpesviridae*. The most common etiological factor is herpesvirus type 2, but a significant proportion of diseases are caused by herpes type 1 and cytomegalovirus. Most often urogenital herpes infection (UHI) affects young people, and the prevalence of genital herpes increases over time [8, 9]. Unfortunately, in Ukraine, due to the lack of mandatory registration of all forms of herpesvirus infection, the total number of patients remains unknown. However, it is possible to draw conclusions about the social significance of this group of diseases, which further motivates researchers to its profound investigation. Thus, in the United States 8.5 - 9.0 million cases of recurrent UHI [10] are registered annually. In Western Europe, the incidence of UHI exceeds 80 cases per 100 thousand of population. In the UK, genital herpes is 7 times more common than syphilis [2].

It is known that in 30 - 50% of those infected with the herpes virus relapses occur during the first 2 - 3 years, and the rate of increase in the total number of patients is higher than population growth [7]. The progression of UHI leads to chronic inflammatory processes in various parts of the urinary system, problems with fertility, potency, and, as a consequence - psychological disorders [8, 11].

To study the effects of herpes infection on the body and understand the interaction between the virus and the human immune system is a top important problem. It is necessary to build a correct idea of the pathogenesis and treatment of patients, and hence increase the effectiveness of care for patients.

According to the results of many studies, herpesvirus infection should be regarded as a systemic lesion of the body with the predominant manifestations of the disease of individual organs [12]. The variety of manifestations of the disease has necessitated the search for common features of pathogenesis and factors that affect its course. The main features of the pathogenesis of herpes infection are:

1. Infection of the sensory ganglia of the autonomic nervous system and lifelong persistence of HSV in them.

2. Defeat of immunocompetent cells, which leads to secondary immunodeficiency, which creates conditions for recurrence of the disease.

3. HSV tropism to epithelial and nerve cells, which causes polymorphism of clinical manifestations of herpes infection.

Thus, pathogenesis main phases are: penetration into epithelial cells; penetration into nerve endings and paravertebral ganglia; subsequent elimination of the virus from tissues and organs (after 2 - 4 weeks); reactivation of HSV and its movement to infection atrium (with a decrease in the body's resistance) [2, 13].

Variants of the disease course are determined by age, sex, infection route, the state of the immune system, the presence of other diseases.

The development of urogenital infection most often occurs in close physical contact with the patient (including the latent form of the disease) or the virus carrier during genital, orogenital, genitorectal and oral anal contact [14, 15]. Only 10% of infected people develop clinical symptoms of primary UHI, the most common option is asymptomatic [16]. There are groups of UHI increased risk development, similar to the groups of risk of infection with viral hepatitis or HIV infection (persons with multiple and casual sexual contact, persons providing commercial sex services, men who have sex with men).

HSV is more likely to cause long-term urethritis, recurrent cystitis, and chronic prostatitis. The frequency of herpetic urethritis (HU) 40 years ago was from 0.3 to 2.9% of all registered non-gonococcal urethritis (Nahmias A. et al., 1976; Ilyin I. I., 1977), which allowed researchers in the 70's to include HU to rare forms of urethritis. The work of later years showed that HU is found in 42.4 - 46.6% of cases in men suffering from recurrent genital herpes (Baluyants E. R, 1991; Semenova T. B., 2000). According to various authors, to day, 2.9 - 21.8% of prostatites are of herpetic etiology [17].

Another important causative agent of the urogenital system diseases in men is cytomegalovirus infection (CMVI) - anthroponotic opportunistic infection, which in most cases has an asymptomatic or mild course. It is dangerous in various immunodeficiency

conditions and pregnancy (due to the risk of fetus's intrauterine infection). The causative agent is a DNA-containing virus *Cytomegalovirus*, the subfamily *Betaherpesvirinae* of *Herpesviridae* family, similar in structure to the HSV. There are 3 strains of the virus: Davis, AD-169 and Kerr. Slow reproduction of the virus in the cell is possible without its damage. Among the various variants of CMV infection subclinical forms and latent viral load dominate, and the symptoms become pronounced in immunodeficiency. A common clinical classification of CMV infection has not been developed. According to one of the classifications, there are congenital CMV infection in acute and chronic forms and acquired CMV infection in latent, acute mononucleosis or generalized forms. Urogenital infections caused by CMV are usually characterized by a prolonged course with a high frequency of chronicity [18].

Nowadays, due to the improvement of diagnostic methods, several pathogens of the urogenital system are often detected at the same time, which complicates the choice of treatment tactics [16]. To diagnosticate recurrent genital herpes under typical clinical manifestations of the disease is easy when examining the patient. Significant complications arise in atypical forms of UGI or in herpetic lesions of the genitourinary tract, when there is no typical lesion of the skin and / or mucous membranes. Careful investigation of complaints and medical history is important in these cases. First of all, the doctor should be wary of the lack of effect of antibacterial treatment in recurrent lesions of the genitourinary tract, accompanied by complaints of itching, burning, slight mucous secretions from the urethra.

Besides, the patients often are subjects to respiratory diseases, sometimes with typical labial or nose alae eruptions, periodical general weakness, malaise, subfebrile temperature, depressive states. Quite often UHI patients indicate unpleasant or painful sensations, and do not always associate them with herpes's exacerbations. Herpes infection of the urogenital system in most cases, even in the absence of specific therapy, has a wavy course, with alternating periods of exacerbation and remission [6, 19].

In some cases, the correct diagnosis is hindered by the presence of a microbial association that masks the manifestations of herpes infection (chlamydia, strepto- and staphylococci, fungal flora, gonococci, pale treponema), which suggests the need for careful examination of patients and timely monitoring of treatment [20]. Existing methods of laboratory diagnosis of herpes simplex are basically divided into two groups:

1) isolation and identification of HSV in cell culture or detection of pathogen antigen from infected material in cytological, immunofluorescent studies, enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR);

2) detection antibodies against HSV in the serum.

Despite the variety of methods, HSV can not always be detected in the patient's biological material, and the frequency of virus release differs from different biological environments [21]. They try to prevent a pseudo-negative result by increasing the number of tested samples in each patient. Thus, a single negative result does not preclude the diagnosis of genital herpes. Virological examination of secretions from the genitourinary system is repeated (2 - 4 times) every week, but the best result to confirm the diagnosis is obtained by a combination of several research methods [22].

The diagnosis of primary herpes infection is facilitated by the detection of IgM and / or a fourfold increase of specific IgG titers in paired sera (the interval between blood sampling is 10 - 12 days). Constant antigenic stimulation in chronic recurrent herpes leads to a steady increase in IgG levels in the patient's blood, with exacerbation of the disease there is an increase in IgM levels.

To confirm the cytomegalovirus etiology of the process, the studies of saliva and urine, as well as material obtained by biopsy and autopsy are most often used. At the same time specific cytomegalic cells typical for a disease come to light.

As in the examination HSV patients, serological methods (ELISA, RIA, RIF and immunoblotting), assessing the levels and dynamics of antibody titers are used. However, the most reliable method is the study of samples by PCR to detect viral DNA [23].

More sophisticated virological methods (isolation of the virus in human fibroblast culture, determination of virus antigen in the test material with monoclonal antibodies) are not widespread in clinical practice.

An important component of further effective treatment of UHI of herpetic etiology is to determine the state of the immune system. The main indicators that determineat these states are the levels of immunocompetent cells, immunoglobulins M and G and phagocytic index. This allows to assess the state of both cellular and humoral immunity. Thus, mature T-3 lymphocytes are responsible in the body for the timeliness and intensity of the immune response, thus maintaining the antigenic stability of the body. Of these, T-4-lymphocytes (helpers) promote the activation of immune processes, and T-8-lymphocytes (suppressors) - their inhibition. Immunoglobulins and their ratio, together with the indicator of phagocytic activity help to assess the severity of the inflammatory process. Phagocytic activity usually increases at the beginning of the inflammatory process and decreases with its chronicity [24].

The results of previous studies suggest that patients with exacerbation of herpes infection are more likely to have immunodeficiency of varying degrees, and some indicators of the immunogram will have values more characteristic of the chronic course of the disease.

The objective. To establish the presence of differences in immunity in urogenital infections caused by different representatives of herpes viruses, including mixed infections, and compare the results obtained with those in the control group. **Materials and methods.** We analyzed the results of the immune status exanimation in urogenital infections patients, treated in 2007 - 2010. 150 men aged 18 - 65 years old were examined (mean age 33.0 ± 2.7). The duration of the disease is from 1 to 10 years, mostly 5 - 7 years. The control group consisted of 30 healthy male volunteers. It this group was comparable in age with the main group (p> 0.05).

The presence of viral infection was confirmed by blood PCR and RIF tests. Immunological studies to determine cellular and humoral immunity were performed according to the method of Lebedeva and Ponyakin [25].

Results. By age, the patients under examination were distributed as follows: 18 - 20 years - 8 (5.3%) patients, 20 - 30 years - 69 (46.0%), 30 - 40 years - 32 (21.3%), 40 -50 years - 24 (16.0%), 50 - 60 years - 17 (11.3%). The analysis of the relevant data shows that young people of reproductive age predominated among patients with UHI, and the share of people aged 20 to 40 years was 67.3% (p <0.05), which coincides with the data of the world literature. 77.3% of the patients under examination had diseases with mixed etiology, in 12% of the subjects herpetic and in 10.7% - cytomegalovirus etiology of the process was diagnosed. In 22% of patients HSV was isolated from the urethra, in 23% it was isolated from prostate juice, in 15% from semen, and in 26% - from urine.

The results of immune status examination are shown in Table 1.

Table 1 - Immune status of patients with urogenital infections of viral etiology (n = 150)

Indexes of immunity Імунітету	Control group, n=30	UHI infection		
		CMV, n=18	Herpetic, n=16	CMV +herpetic, n=116
CD-3-T-lymphocytes, %	64,0±6,3	45,2±1,2*	60,1±3,1	34,3±2,2*
CD-4-T-helpers, %	42,0±6,8	56,1±1,3	48,2±1,8	36,2±1,4
CD-8-T-suppressors, %	16,5±5,1	20,1±2,7	25,1±1,8*	27,3±1,7*
Phagocytic index	68,0±8,2	26,0±2,3*	23,0±0,8*	16,0±0,7*
Ig M (g/l)	0,8±0,2	0,9±0,1	2,1±0,2*	0,8±0,1
Ig G (g/l)	13,9±2,5	12,0±1,3	15,0±1,8	10,0±1,2

Note: * - statistical significance, p<0,05

According to the data shown in table 1, there are changes in immune status, the largest in patients with mixed infection, in comparison with the control group In particular, it is in this group the lowest rates of CD-3-T-lymphocytes and phagocytic index with a simultaneous increase CD-8-T-suppressors level. A decrease in the proportion of CD-3-T lymphocytes of varying degrees, i. e. a deficiency of cellular immunity, was registered in all patients with UHI, while a decrease of CD-4-T-helpers - the main regulators of the immune response - was observed only in patients with mixed infection. This may indicate potentiation of the negative effects of pathogenic viruses on the patient's immune system. A significant decrease in the phagocytic index in the groups under examination, compared with the control, most likely can confirm the presence of chronic inflammation. The smallest differences compared with the control are observed in immunoglobulins M and G. Significant increase in IgM indicates dysfunction of the humoral part of the immune response.

Conclusions and recommendations. Thus, in herpetic, cytomegalovirus or mixed etiology of UHI patients, imbalance between individual parts of the immune system is determined. This indicates a decrease in the immunobiological qualities of the body and the chronicity of the infection. The data obtained indicate the presence of defects in immune protection in viral lesions of the urogenital system patients, especially in cases of combined infection. There is a decrease in cellular immunity with the formation of secondary immunodeficiency, which contributes to the further progression of the process.

When a lesion of the urogenital sphere of cytomegalovirus or herpetic etiology is diagnosed, it is necessary to conduct an additional study of the patient's immune status. This recommendation is especially relevant for persons with frequent relapses or a significant degree of damage. The establishment of immune defense defects will allow timely supplementation of the disease with immunomodulatory drugs, which will accelerate recovery and increase the effectiveness of treatment.

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