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HPV (HUMAN PAPILLOMAVIRUS INFECTION): CLINICAL OBSERVATION AND PREVENTION

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Abstract:

Papillomaviruses belong to the Papovaviridae family and have been parasitizing humans for thousands of years. These are small, non-enveloped 20-sided DNA viruses that infect epithelial cells of different anatomical zones.

Keywords: Human papillomaviruses, therapeutic vaccines, oncogenic HPV types, genital warts, papillomatosis, suppression of local immunity, Tiloron.

Papillomaviruses belong to the Papovaviridae family and have been parasitizing humans for thousands of years. These are small, non-enveloped 20-sided DNA viruses that infect epithelial cells of different anatomical zones. Human papillomaviruses (HPV) are classified into five evolutionary groups: alpha, beta, gamma, mu, and nu. Representatives of the alpha group affect the genital tract, and the rest only the skin. The diameter of the virus is 55 nm, the HPV genome is represented by a long double-stranded circular DNA with a size of 8 thousand base pairs. Depending on the time of expression, HPV genes are divided into early and late, respectively, they encode early E1-E7 and late L1 and L2 proteins.

It is very difficult to estimate the prevalence of human papillomavirus infection (HPV) among the population. It is estimated that genital warts occur in approximately 1% of the sexually active population, and in 5–40% the infection is subclinical or asymptomatic. In pregnant women, the detection rate for all types of HPV is 30–65%, and for types of high oncogenic risk — 20–30% [1].

The most common route of transmission is direct contact with the skin or mucous membrane of a sick person or virus carrier. The virus remains viable in water (pool, bath), and is also transmitted through sexual intercourse. Papillomaviruses, which infect the skin and mucous membranes of the anogenital tract, are one of the most common sexually transmitted infections that women and men encounter in the early years of sexual activity. The peak of HPV infection worldwide is between 17 and 25 years, then the prevalence of infection declines and rises again at the age of 35–44 or 45–54 years. This likely reflects the growing social trend of divorce and new partnerships that form at an older age. Risk factors for PVI infection are other sexually transmitted infections (STIs), oral contraceptive use, smoking, and a lack of cellular immunity in infected individuals. In 1989, the vertical transmission of the virus was proved, which is confirmed by reports of the detection of HPV in the amniotic fluid of pregnant women and in children born to mothers carrying HPV [2]. Possible risk varies according to different authors from 3% to 80% [3]. This spread is explained by differences in the method of polymerase chain reaction (PCR) for the detection of HPV DNA. In this case, PVI can be transmitted transplacentally and intrapartum (in particular, HPV 6 and 11)). The risk of infection is directly proportional to the severity of infection (the number of viral particles) and the time of the anhydrous interval in labor, however, studies have shown that delivery by caesarean section does not reduce the risk of fetal infection, which indicates predominantly intrauterine infection [2]. Intrapartum infection can lead to juvenile recurrent respiratory papillomatosis (the incidence is 1.7–2.6 per 100,000 children and 1 per 1,500 births among women with genital PVI) [4]. All statistical studies that have been carried out unambiguously indicate that the only way to acquire oncogenic HPV types affecting the genitals is through the genital tract [5].

Taking into account the tropism, HPV is divided into mucotropic and dermotropic. Depending on carcinogenicity, known papillomaviruses can be conditionally divided into three main groups: non-oncogenic (HPV 1, 2, 3, 5, 10, 63), low oncogenic risk (mainly HPV 6, 11, 42, 43, 44), high oncogenic risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). Differences in the oncogenic properties of HPV are associated with the ability of certain types of viruses to determine the number of mitoses in affected cells.

The human papillomavirus is characterized by a wide range of epithelial proliferative lesions. Hyperplasia and hyperkeratosis as the main pathomorphological and clinical manifestations of skin infection caused by HPV, as well as the extent and depth of the lesions, depend on the type of virus. HPV types

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1, 2, 4 and 63 can cause vulgar and plantar warts. Flat warts can be caused by HPV types 3, 10, 28, 41, 49, and 75. Among dermatotropic viruses, a subgroup of viruses associated with epidermodysplasia verruciform and actinic keratomas was identified: types 5, 8, 9, 12, 14, 15, 17, 19-25, 36, 46, and 47. HPV types 5 and 8 were identified as a cause of the development of squamous cell carcinoma in patients with epidermodysplasia verruciform [6, 7]. In patients with recurrent respiratory papillomatosis, HPV of the 6th and / or 11th type is more often found.

To date, there are about 40 genital HPV types. The cause of genital warts (genital warts) in 90% of cases is the 6th and 11th types of papillomavirus. It has been shown that dysplastic processes of the cervix most often develop against the background of persistent genital infections, the greatest role of which is attributed to HPV [8, 9]. Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 may be the cause of cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), cancer of the larynx. Cervical cancer is one of the few types of malignant neoplasms with an established etiology of the disease. For the discovery of the role of HPV in the development of cervical cancer, the German scientist Harald zur Hausen was awarded the Nobel Prize in Medicine and Physiology in 2008. About 0.5 million new cases of cervical cancer are registered in the world every year, and according to experts, in the absence of active intervention, by 2020 this number will increase by more than 700,000 cases [10].

The long latency period of infection, the development of cancer in only some infected with PVI give reason to believe that, in addition to the persistence of the HPV genome, a violation of the structure and function of cellular genes is a necessary condition for the development of cancer. Mutations in various regions of the E1-E2 gene, which is normally responsible for the episomal status of HPV DNA, act as an initiating factor. As a result of damage to E1, the HPV genome integrates into the chromosomes of the host cell. Since E1-E2 regulate and control viral transcription, their destruction ends in uncontrolled expression of the E6-E7 genes, which directly trigger the processes of tumor transformation. The oncogenic properties of E6-E7 products are due to their ability to form complexes with proteins p53 (for E6) and pRb (for E7). When the normal functions of p53 change, the cell that should have died begins to divide uncontrollably, forming tumor-like growth. In the pathogenesis of carcinogenesis, local immunity is suppressed due to the synthesis of the viral oncoprotein E7. The E7 protein neutralizes the antiviral and antitumor activity of interferon alpha-2 due to its ability to selectively block most genes induced by interferon, nullifying all efforts of interferon therapy. Also, the E7 protein inhibits the expression of genes of the main histocompatibility complex, making it difficult for the host immune system to recognize tumor cells. The biological properties and molecular structure of HPV proteins have been studied quite fully, however, specific ways of realizing the carcinogenic effect of the virus require further clarification. In patients infected with the most aggressive HPV variants, as well as those with genetic, hormonal, immune and other cofactors, PVI will develop to precancerous conditions and may progress to cancer.

The incubation period of PVI ranges from 1 to 12 months (on average, 3 months). Clinical manifestations of PVI of the genitals can be different: genital warts, papillomas with exophytic growth, flat papillomas. Condylomas are warty eminences, which can be single, but more often multiple, merged into groups and resembling cauliflower or rooster combs. Their surface is covered with stratified squamous epithelium, often with keratinization. A particularly rapid growth of genital warts is observed during pregnancy, in adolescents and in HIV-infected individuals (the development of a giant Buschke-Levenshtein tumor). It is quite natural that the epidemic of HPV infection in adults could not but affect the increase in the incidence of anogenital warts among children. The data of modern methods have shown that papillomavirus lesions in children are associated with the same types of HPV as in adults, but due to physiological characteristics and immaturity of defense mechanisms, children and adolescents are more vulnerable than adults.

Subclinical forms are represented by intraepithelial papillomas with endophytic growth. Cervical papillomas are usually flat or intraepithelial ("atypical"). Revealed by colposcopy, cytological and histological studies. The severity of the course and the rate of regression is determined by the type of HPV.

However, anogenital warts only form the tip of the iceberg called HPV infection. The majority of clinical cases are presented by patients with a latent form of HPV infection, in whom HPV is often accidentally diagnosed during PCR diagnostics or oncocytological examination of scrapings from the cervical canal (signs of koilocytic atypia).

When passing through an infected birth canal, it is possible to infect a child with PVI with the development of juvenile recurrent respiratory papillomatosis. The clinical picture of respiratory papillomatosis consists of voice and breathing

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disorders. Most often, with damage to the larynx in the area of the commissure and the anterior sections of the vocal folds, hoarseness of the voice develops, up to its complete loss. As the lumen of the larynx narrows with papillomas, stenosis develops, death from asphyxia is possible. The pathological process in childhood is active, it is characterized by the prevalence and frequency of recurrence, and therefore children undergo multiple surgical interventions in order to remove papillomas. Multiple repeated excision of laryngeal tumors leads to the development of cicatricial complications, the need for tracheostomy, loss of the ability to speak, and aggravation of chronic respiratory hypoxemia. With the progression and spread of the tumor into the distal airways, the disease is often fatal.

Clinical diagnosis of genital warts and papillomas usually does not cause difficulties, if this is not an early stage of the disease, when the formations are small, or not an "atypical" form of PVI. But even with an undoubted clinic, HPV infection must be laboratory confirmed. The main diagnostic method is cytological. The detection of coilocytes, transepithelial lymphocytic infiltration, and basal cell hyperplasia in a biopsy specimen is considered confirmation of PVI of the genitals. The determination of DNA of 12 types of HPV of high oncogenic risk by the method of polymerase chain reaction (PCR) in real time (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) in cervical scraping is widely used. channel, urethra or urine. The method of nucleic acid amplification (NAA) is being introduced into practice. Serological diagnostic method is the detection of antibodies against virus-specific proteins E2, E6 and E7, the presence of which is a marker of current infection. For this, ELISA is used - a test with highly purified recombinant proteins E6 and E7. A decrease in the concentration of these antibodies is an indicator of successful therapy for PVI and cervical neoplasias.

It was found that the regression of HPV-induced damage directly depends on the state of T-cell immunity and neutralizing antibodies block the spread of viral infection. And although HPV-related formations often self-regress, in many, especially in people with immunodeficiencies, PVI becomes persistent and is capable of reinfection. HPV resistance to treatment is associated with a structural feature of the virus, which allows it to persist for a long time in the body, exacerbating the existing secondary immunodeficiency. The complex cycle of intranuclear replication, the possibility of the existence of infection in episomal and integrated forms, the difficulties of studying the pathogenesis of the virus on biological models, determine the absence of pathogenetic therapy for PVI today [11].

In accordance with the management "Clinical recommendations. Dermato -venereology "ed. A.A.Kubanova (2010) and the European guidelines for the treatment of STIs, the therapy of HPV infection manifestations must meet the following requirements: destruction, prevention of complications, reduction in the number of relapses, and improvement in the quality of life of patients. Since there is no method for eliminating HPV, treatment is aimed at eliminating the clinical signs of HPV: any types of warts or cervical pathology in the presence of atypical cells in smears and biopsies. Traditional methods of treating warts are well known and include cryo-, electro-, radio wave and laser surgery, as well as treatment with cytotoxic (podophyllin, podophyllotoxin, 5-fluorouracil), chemicals (Solkoderm, Verrukacid, Duofil, etc.), causing cytolysis and tissue necrosis [13]. Currently, the most effective, especially with extensive rashes and a recurrent course of the disease, including in pediatric practice, is the use of combined methods of therapy - the combined use of physical, chemical or drug methods, which includes local treatment and the use of various systemic nonspecific antiviral (Lavomax) and immunomodulatory drugs (interferons and interferon inducers) [12, 13]. So, for the treatment of respiratory papillomatosis in children, cryodestruction, endolaryngeal phonophoresis of cytostatics, photodynamic therapy, interferon therapy (interferon alpha-2), immunocorrective therapy (muramilpeptide) are used. The use of therapeutic vaccines could be a promising method in the treatment of clinical manifestations of HPV. The disadvantage of vaccine therapy is its narrow therapeutic effect, while about 40 HPV strains parasitize the genitals. Consequently, the agenda does not remove the need for a therapeutic method that has the property of eliminating the virus. Therefore, a search is under way for new agents, including interferon inducers, for the treatment of genital warts and other clinical manifestations of HPV.

Adequate immunotherapy contributes to the suppression of HPV activity, reducing the frequency of relapses, and its elimination. Among other well-studied drugs used in the complex treatment of PVI, interferon alpha-2, 5% imiquimod, inosine pranobex, indole-3-carbinol (Indinol, Promisan) are used in clinical practice. It recommended inside - focal administration of interferons, especially in case of immunodeficiency or systemic administration for 4 weeks. Clinical data indicate a high efficiency of the combination of laser therapy with local application of interferons or interferon inducers. Thus, the use of CO2 laser excision

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of anogenital genital warts in children is a safe, relatively atraumatic and effective treatment method [15]. For the treatment of pregnant women, physical destructive methods are recommended: CO2 laser, radio knife, cryotherapy.

HPV is a genetically stable DNA virus, so the likelihood of its genetic transformation is negligible. Genetic stability means that infection with this virus can be prevented long-term by vaccination. In 2006, the US Food and Drug Administration (FDA) registered the world's first quadrivalent vaccine, Gardasil, which has been shown to be effective in preventing infection with the leading HPV types (6/11/16/18). In addition to protection against the four vaccine types, Gardasil provides partial cross-protection against persistent infection and cervical lesions caused by ten high-risk non-vaccine HPV types, including HPV 31, 33, 35, 45, 52 and 58, which are phylogenetically related to HPV 16 and 18. Currently, the quadrivalent vaccine is registered and used in more than 130 countries around the world. In 2008, a bivalent vaccine Cervarix was also registered, containing two types of HPV L1 capsid proteins - 16 and 18. In the context of prevention, the best results can be achieved by combining screening screening programs with the widespread reasonable organization of routine voluntary vaccination of the population, especially of certain medical and social contingents (adolescents from the group of risky behavior, sexually active women taking combined oral contraceptives, persons with immunodeficiency of various origins).

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