SOME ASPECTS OF THE ROLE OF HUMAN PAPILLOMAVIRUS INFECTION IN THE DEVELOPMENT OF CERVICAL DYSPLASIA

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Abstract. *The detection of HPV infection during a preventive examination of healthy women and patients with dysplastic changes in the cervical mucosa is still at the outpatient stage, and adequate antiviral therapy in these women can serve as an effective pathogenetic prevention of precancerous and tumor diseases of the cervix uteri According to the results of the study. Treatment regimens have been developed and implemented in patients with identified HPV infection with a constant cervix, as well as in the presence of background and precancerous diseases of the cervix.*

Keywords*: cervix; HPV infection; dysplasia; precancerous diseases; carcinogens.*

Introduction

Human papillomavirus (HPV) is a group of extremely common and genetically heterogeneous DNA viruses that infect the epithelium of the skin and mucous membranes. Historically, HPV has been infecting humans for a long time. Warts, both on the hands and plantar, were known as early as the time of the ancient Greeks and Romans, and external anogenital warts are mentioned even in earlier documents. Using the polymerase chain reaction, it was possible to isolate HPV 18 DNA from a mummy of the 16th century. Mary of Aragon (1503-1568). Only at the beginning of the XXI century. humans have the opportunity to significantly influence the spread of HPV. The famous German scientist Harald zur Hausen discovered the connection between the human papillomavirus and the development of cancer, which made it possible to focus on the creation of vaccines that can prevent HPV-associated diseases. [3]

Human papillomaviruses infecting epithelial cells of the skin and mucous membranes are etiologically associated with the development of pathological changes in the cervix and, in fact, cervical cancer, as well as anogenital warts (condylomas) and recurrent respiratory papillomatosis. In addition, HPV is associated with other malignant neoplasms - squamous cell carcinoma of the anus, vulva, vagina, penis, and head and neck. To date, approximately 130 different types of HPV have been described and well-studied. An even larger number of representatives have been partially studied and can subsequently be attributed to new types of HPV. Approximately 30–40 types of pathogen infect the anogenital area, of which 15–20 associated with cancer are classified as high risk and about 10–15 associated with genital warts (warts) and other benign lesions are classified as low risk. It has been proven that up to 70% of cervical and anal cancer cases are caused by highly oncogenic HPV types 16 and 18, and more than 90% of anogenital warts are caused by HPV 6 and 11. The mechanism of cancer development is associated with the expression of HPV E7 and E6 proteins. which inactivate the retinoblastoma protein and destroy the p53 protein, which leads, respectively, to uncontrolled cell division and the accumulation of mutations in cellular DNA. After natural infection with HPV, a low rate of seroconversion and a low level of production of antibodies to HPV are noted: as a rule,

antibodies formed after infection with one type of pathogen do not prevent infection with other types of HPV [3]

Modern data on molecular oncology have shown with sufficient conviction that dysplastic (precancerous) changes in stratified squamous epithelium (MPE) of the vaginal part of the cervix (varying severity of MPE dysplasia, flat warts) are caused by human papillomavirus (HPV) of various genotypes. The main mechanism of viral carcinogenesis is the inclusion of DNA of one of the HPV genotypes containing quality information (mainly genotypes 16,18) into the genome of a normal cell, which can cause its tumor transformation and, over time, progression into pre- and invasive cervical cancer.

Taking these data into account, it becomes clear that the detection of HPV infection during the preventive examination of healthy women and in patients with dysplastic changes in the cervical mucosa even at the outpatient stage, and adequate antiviral therapy in these women can serve as an effective pathogenetic prevention of precancerous and neoplastic diseases of the cervix. ...

With the introduction of the polymerase chain reaction (PCR) technique into medical practice, it became possible to determine the viral DNA of human papilloma, which has carcinogenic properties. The ego, in turn, made it possible to conduct this study [1,2,3].

To date, the frequency of the prevalence of HPV among women of reproductive age living in Uzbekistan has not been established and, naturally, effective methods of diagnosing and treating this pathology related to sexually transmitted infections have not been worked out [4,5,6].

However, it is necessary to note a number of issues that remain poorly covered or generally little studied and require clarification. For example, little has been studied issues related to the possible pathological role of untreated long-term ectopic and background diseases of the cervical mucosa in the development of chronic persistence of HPV infection, which ultimately lead to the development of dysplasia and cervical cancer after many years.

Most studies on HPV infection are based on traditional cytological screening, while the technical capabilities of molecular genetic research methods have now significantly increased and can be reliably included in screening programs for the detection of HPV infection, thereby dramatically increasing their sensitivity and specificity [7,8 ,9].

Purpose of the study

To study the prevalence of human papillomavirus (HPV) infection among women of reproductive age and to develop, on the basis of the data obtained, a pathogenetically substantiated, effective complex of diagnostic and therapeutic measures.

Material and methods

Taking into account the objectives of this study, cytological examination, gynecological examination and ultrasound examination of the pelvic organs were carried out in 1856 women of reproductive age who applied to the antenatal clinics in Tashkent for various reasons. Patients who were found to have severe chronic inflammatory processes in the small pelvis, ovarian cysts, neoplasms, including uterine fibroids exceeding the size of 6-7 weeks of gestation, were not included in this study. This group of patients, consisting of 210 women, was excluded from the screening group and was not included in further analysis.

Thus, the material of this projective study is presented by the data of a survey of 1444 women of reproductive age living in our region and working at several industrial enterprises of the city (screening group). At the first stage of cytological screening, these patients were divided into

three groups: Group I (the cervix was not visually changed), Group II - dysplasia of varying severity was determined, Group III (comparison group or "promiscuous" group)

At the first stage, women were questioned, examined by a gynecologist (taking smears from the mucous membrane of the ecto-endocervix with a "cyto-brush" brush on two glasses, followed by drying them, treating them with alcohol and staining "hematoxylin - eosin"), followed by cytological examination. Additionally, after taking smears, a small scraping was taken from the surface of the endocervix and urethra with a Volkmann spoon for analysis for HPV by polymerase chain reaction. Examination by a gynecologist was complemented by an examination of the mammary glands and ultrasound examination of the pelvic organs.

At the second stage of screening, an in-depth examination was carried out of 622 women with identified pathology of the cervix, with signs of HPV infection.

Results and discussion

Amplification of HPV DNA (increase in the number of copies of viral DNA) using oligonucleotide primers ("amplimers") makes it easy to detect the HPV genome in the test material, even if it is present in a minimal amount, the exponential increase in the number of copies of the HPV genome during PCR provides high sensitivity of the method and allows you to carry out a significant number of analyzes in a short time (2-4 hours). HPV infection was diagnosed by PCR in the genetic engineering laboratory of the Institute of Genetics and Experimental Plant Biology of the Academy of Sciences of the Republic of Uzbekistan.

In total, using polymerase chain reaction (PCR), the frequency of detection of human papillomavirus (HPV) and its genotype were studied in 653 examined women of the indicated groups.

The material for the study was scrapings of the mucous membrane of the urethra and endocervix, from which the total DNA fraction was isolated using a standard protocol. Analysis of the product of this PCR made it possible to type HPV for low oncogenic (6,11) and high oncogenic (16, 18) viral genotypes.

Highly oncogenic genotypes (genotypes 16 and 18) of HPV were detected in group I in 69.2% of cases, in group II - 71.4% of cases and in group III in 76% of cases. Thus, highly oncogenic HPV genotypes were identified in 469 (71.8%) women out of 653 examined by PCR.

Low-oncogenic HPV genotypes (6, 11 genotypes), not associated with malignant transformation of the cervical IHO, were detected in 68 (10.4%) women, in group I in 6.8% of cases, in group II in 16.2% of cases and in group III in 7.4% of cases.

Undifferentiated HPV genotypes were detected in 116 (17.8%) patients. This category of conclusions presents the greatest difficulties in terms of developing therapeutic tactics, requiring the observation of the patient for repeated studies.

Further analysis of the data showed that HPV infection was significantly more frequently detected in patients with dysplasia combined with underlying cervical diseases (P * 0.01); in the remaining samples, the increase in the frequency of HPV infection was in the nature of a trend (P = OD).

To clarify the complex problem of coincidences of cytological and histological diagnoses, in relation to the pathology of the cervix, at the second stage of this fragment of the work, 93 patients with dysplastic changes in the MPE established by cytological examination (58 patients with cervical dysplasia and signs of HPV infection, 28 patients with dysplasia, but no signs of HPV infection and in 7 patients with preinvasive cervical cancer and cytological signs of HPV infection), electrosurgical conization of the cervix was performed, which made it possible to combine the information content of

cytological conclusions regarding pathological changes in the endocervix with the data of histological examination of the remote “cone” of the cervix uterus.

The presence of foci of ectopia, characteristic of patients with background processes of the cervix, serves as a place of persistence of HPV, which has a tropism for the columnar epithelium. An additional argument in favor of this opinion is the data that HPV initially persists episomally in the cell, i.e. without invading its genomic apparatus.

Upon completion of the screening program, patients with diagnosed HPV infection and associated cervical pathology were treated in order to eliminate dysplastic changes in the mucous membrane and prevent the development of precancerous and tumor changes in the cervix.

427 patients underwent various types of therapeutic interventions, systemic and local, or their combination, aimed at eliminating HPV infection and normalizing the state of the cervical mucosa. In second place in terms of frequency of use was drug treatment of HPV infection with Neovir, which was carried out in 107 women. Neovir was administered at 250 mg, intramuscularly, every other day. One course consisted of 5-7 injections. The intervals between courses are 10-14 days. The treatment was carried out in three to five courses.

Neovir has antiviral effect against DNA and RNA genomic viruses in therapeutic and prophylactic use. The criterion for the cure of papillomavirus infection was the absence of cytological data on the presence of HPV, confirmed by PCR data. The partial effect of treatment was assessed when one of the research methods continued to detect HPV, and no effect if HIV infection continued to be determined by both methods, 20-30 days after completion of treatment.

The greatest effectiveness of therapy was achieved during three courses of treatment - in 85 (92.4%) in 92 patients. When two courses were carried out, the effectiveness was quite high - in 7 (70%) out of 10 patients, but significantly lower than with three courses. ($x2 = 19.6$, $P = 0.05$). One course of treatment gave practically no stable cure.

From the data presented, it follows that two or three courses of treatment for HPV infection is the most effective.

Conclusions

1. When conducting cytological screening of gynecological oncological pathology in women in the reproductive period without visible signs of cervical pathology, a relatively high frequency of detecting latent HPV infection (17.1%) in the general population was established.

2. At the same time, in patients with dysplasia and background diseases of the cervix, the frequency of HPV detection was determined significantly higher (76.2%) than in patients with dysplasia, but without background processes in the area of the ectocervix (4.0%) (P «0 , 01).

3. The use of combined surgical and preparative viral treatment with Neovir gives high results in the treatment of HPV infection and associated pathological processes in the MHTE of the cervix, which in turn led to a decrease in the incidence of cervical cancer.

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