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HUMAN PAPILLOMAVIRUS, CLINICAL, DERMATOLOGICAL AND GYNECOLOGICAL APPROACH

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ABSTRACT

Introduction: *Human papillomavirus (HPV) infection is associated with a wide range of cutaneous and mucosal manifestations. The spectrum of HPV ranges from inapparent infections, through multiple benign clinical presentations, including cutaneous and mucosal disease, to malignant and premalignant conditions. Cervical cancer is the fourth cancer with the highest incidence in women in the world, being the second cause of cancer death in women between 15 and 44 years of age, one of the risk factors for this cancer is the human papillomavirus.*

Objective: *to detail the current information related to human papillomavirus, description, etiology, epidemiology, pathophysiology, anamnesis, physical examination, evaluation, treatment, differential diagnosis, prognosis, prevention and complications taking into account a clinical, dermatological and gynecological approach.*

Methodology: *a total of 27 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 18 bibliographies were used because the other articles were not relevant for this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: human papillomavirus, HPV, dermatosis, warts, infection, papanicolau, tumor virus infections.*

Results: *HPV has been associated with the development of laryngeal, mouth, lung and anogenital cancers. Subtypes 6 and 11 are low risk and are usually associated with the formation of condylomas and low-grade precancerous lesions. Subtypes 16 and 18 are high-risk and are responsible for high-grade intraepithelial lesions that progress to malignant neoplasia. There are more than 180*

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HPV subtypes.The prevalence of genital HPV in adults aged 18-59 years is about 45.2% in males and 39.9% in females. The prevalence of high oncogenic risk HPV genotypes is 2.26%; (95%CI: 1.75-2.78), with the most common genotype being 16 (28.89%). Cervical cancer screening with cytology has significantly reduced the incidence and mortality of this type of cancer in developed countries, despite the fact that its sensitivity for detecting CIN2+ is around 66%.

Conclusions: *it is of remarkable importance to know the human papillomavirus outlook, especially because it is linked to a number of underlying clinical manifestations both benign, premalignant and malignant conditions. The authors recommend prevention, especially suggesting that boys and girls be vaccinated against HPV starting at 11 to 12 years of age, in addition to the other measures outlined in the article. It is important to understand that HPV alone does not cause cancer, but requires triggering factors such as smoking, folate deficiency, exposure to ultraviolet light, immunosuppression and pregnancy. Individuals with cutaneous warts have numerous treatment alternatives available, including surgical removal, cryotherapy, irritant or immunomodulatory drugs, and laser removal.*

KEY WORDS: *HPV, infection, pap smear, warts.*

INTRODUCTION

Human papillomavirus (HPV) infection is associated with a wide range of cutaneous and mucosal manifestations. The spectrum of HPV ranges from inapparent infections through multiple benign clinical presentations, including cutaneous and mucosal disease, to malignant and premalignant conditions. Human papillomavirus (HPV) is the initiator behind various epithelial lesions and cancers, mostly on cutaneous and mucosal surfaces. There are more than 100 subtypes of HPV. Individuals with persistent HPV infection and individuals with multiple sexual partners have a very high risk of displaying more HPV subtypes. HPV infection can be divided as follows:

- Non-genital (cutaneous).
- Mucosal or anogenital.
- Epidermodysplasia verruciformis (EV).

Clinical lesions may be visibly obvious, however some of the latent lesions may require viral DNA testing. Most HPV infections are latent and many of the clinical lesions appear as warts rather than as a malignant neoplasm.

Cervical cancer is the fourth cancer with the highest incidence in women in the world, being the second cause of cancer death in women between 15 and 44 years, one of the risk factors for this cancer is the human papillomavirus; in the literature it is found that serotypes 16, 18, 31, 33, 33, 35, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are strongly associated with CIN and invasive cancer(1-3).

HPV has been associated with the development of laryngeal, mouth, lung and anogenital cancers. Subtypes 6 and 11 are low risk and usually involve the formation of condylomas and low-grade precancerous lesions. Subtypes 16 and 18 are high-risk and are responsible for high-grade intraepithelial lesions that progress to malignant neoplasia. It is important to understand that HPV alone does not cause cancer, but requires triggering factors such as smoking, folate deficiency, exposure to ultraviolet light, immunosuppression and pregnancy(2,4-6).

METHODOLOGY

A total of 27 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 18 bibliographies were used because the information collected was not sufficiently important to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: human papillomavirus, HPV, dermatosis, warts, infection, papanicolaou, tumor virus infections.

The choice of bibliography exposes elements related to human papillomavirus, description, etiology, epidemiology, pathophysiology, anamnesis, physical examination, evaluation, treatment, differential diagnosis, prognosis, prevention and complications taking into account a clinical, dermatological and gynecological approach.

DEVELOPMENT

Etiology

HPV is a circular, double-stranded, non-enveloped DNA virus of the Papillomaviridae family, which enters the epithelium through skin or mucosal disruption and infects basal stem cells. Its genome presents seven early-phase (E) and two late-phase (L) genes of importance for viral propagation. The viral DNA can remain as an independent episome in the period before integrating into the host genome. HPV predominantly integrates at fragile sites in human DNA where the strand is prone to breakage. There are some risk factors related to HPV such as: sexual activity, age at first intercourse and number of sexual partners, smoking, use of oral contraceptives for more than 5 years, betel nut chewing, as well as exposure to radiation and ultraviolet light(2,7).

Epidemiology

HPV subtypes show a predilection for the body sites they infect most commonly and the disease characteristics that reflect infection can be altered. There are more than 180 HPV subtypes. Cutaneous warts of the hands and feet, such as verruca vulgaris or plantar warts, are mostly caused by HPV subtypes 1, 2, 4, 27 or 57. Most anogenital warts, such as condyloma acuminatum, are caused by HPV subtypes 6 or 11 and are called low-risk HPV; these are also responsible for recurrent juvenile and adult respiratory papillomatosis. Precancerous and cancerous lesions of the cervix, male and female anogenital surfaces and the oropharyngeal area are most commonly caused by HPV subtypes 16 and 18. However, subtypes 31, 33, 35, 45, 52 and 58 also fall into the group of high-risk HPVs because they are associated with the development of cervical cancer.

The HPV subclasses that give rise to skin warts are transmitted by contact between skin with microscopic or macroscopic epidermal damage and an HPV harboring fomites. The

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prototypical area for contracting warts on the feet is a locker room.

Low-risk HPV as well as high-risk HPV are considered sexually transmitted, but can be spread through other forms of intimate contact. According to the Centers for Disease Control and Prevention (CDC), the prevalence of genital HPV in adults aged 18-59 years is about 45.2% in males and 39.9% in females(2,8).

The prevalence of HPV infection found in other studies is 2.71% (95%CI: 2.15-3.27). The prevalence of HPV genotypes of high oncogenic risk is 2.26% (95%CI: 1.75-2.78), with the most common genotype being 16 (28.89%). More than 50% of the women were positive for a non-vaccine-positive high-risk genotype: 51 (18.89%) or 58 (13.33%) or 68 (12.22%) or 31 (11.11%). About 23.33% of women coexisted at least 2 non-vaccineable high-risk genotypes. Younger women (≤ 30 years) were 2 times more at risk of infection with any HPV: OR 2.01; (95%CI: 1.02-3.96); and 2 times more likely to use hormonal contraceptives vs. preservative: OR 2.09; (95%CI: 1.64-2.67)(9).

Pathophysiology and Histology

The E 6 and E 7 oncoproteins inactivate the p53 and pRb proteins, causing cell cycle dysregulation and neoplastic transformation of the affected tissue. The virus remains relatively inactive in early infection, not allowing the cell to enter a resting state (G0). As infected cells grow and mature, E 2 regulates the transition from early- to late-phase genes, and the virus increases virion production for dispersal. This increased virion manufacture in HPV-generated lesions characteristically shows up as hypertrophy of the infected tissue with the potential for atypia and malignant transformation in those lesions infected with high-risk HPV. Histology of the wart may reveal hyperkeratosis, papillomatosis and parakeratosis. Long intercalary ridges usually show towards the center of the wart and capillaries are often thrombosed (2).

Anamnesis and Physical Examination

The assessment and treatment of HPV infection changes according to the site of the affected body and the characteristics of the disease. Within the anamnesis, several situations should be investigated. In cutaneous warts (verruca vulgaris, plantar warts), you can ask about possible infectious contacts and hygiene habits such as the use of flip-flops when taking a shower at the gym or if the lesions are painful or prone to bleeding. In anogenital warts such as condyloma acuminatum, you could ask about sexual history/infectious contacts, duration and location of the wart, if you have ever had HPV vaccination (Gardasil, Cervarix), history of wart removal or treatment, as well as diseases or medications that may cause immunosuppression. In addition, you can ask about Pap smears (cervical for women, anal for men), HPV tests and sexually transmitted infections. In cervical squamous and glandular dysplasia, you can ask about menstruation, previous Pap smears, HPV test, sexually transmitted infections or sexual history or infectious contacts, previous HPV vaccination and any related symptoms, such as bleeding, spotting outside menstruation, pelvic or genital pain, pain or bleeding during sexual intercourse and/or palpable lesions in the cervix.

Within the physical examination it is important to perform the following actions in the following encounters. In cutaneous warts (verruca vulgaris, plantar warts) the hands and feet should be thoroughly examined, including between the fingers and the lower part of the fingers. In anogenital warts such as condyloma acuminatum, the anogenital region should be examined. Individuals may also need a speculum examination of the vaginal walls and/or anus. Males may occasionally need an examination of the urethra. Depending on the history of sexual practices, an oropharyngeal examination may be prudent. If squamous or glandular cervical dysplasia is found, a speculum examination of the cervix should be performed. Depending on the age of the affected person and history of Pap smears, an initial Pap smear or a second Pap smear may be required.

Epidermodysplasia verruciformis is an autosomal recessive disorder that increases susceptibility to specific warts not usually seen in the general population. EV is also seen in immunocompromised individuals and those who have undergone transplantation. The condition begins in childhood and can involve any area of the body. The warts are flat and are usually mistaken for tinea versicolor. These warts have a low metastatic potential and are locally destructive.

Evaluation

Individuals with cutaneous, anogenital and/or oropharyngeal warts may have them removed and sent for histopathologic examination when there is any uncertainty about the diagnosis or concern for dysplasia.

Screening for cervical dysplasia/malignancy is commonly done through a speculum exam and a Pap test with a simultaneous or reflex HPV test, a screening test that is done on cervical cells to assess the most common HPV subtypes associated with dysplasia. Treatment protocols stratify affected individuals by age, HPV status and Pap test results. Based on management stratification, compromised patients with results linked to squamous or glandular intraepithelial lesions may be directed to colposcopy(10).

HPV in Pregnancy

Hormonal changes that occur in pregnancy temporarily interfere with the immune response, which could impact HPV replication/depuration. Therefore, an increase in the frequency and progression of genital lesions caused by HPV in the gestational period is to be expected. In comparison to GW, typical condylomatous lesions may be normochromatic, erythematous or brownish with a rough surface, and may be flat, papular or pedunculated. They are commonly seen near the vaginal introitus, however, they can be seen in multiple locations, such as the cervix, urethra, perineum, or intrarectal region. GWs can proliferate and become friable during pregnancy. In these affected women, lesions may be larger, more numerous, resistant to treatment or recurrent(3,11).

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Treatment

Individuals with cutaneous warts have numerous treatment alternatives available, including surgical removal, cryotherapy (freezing the infected tissue), irritant or immunomodulatory medications, and laser removal. The overall goal of many of these treatments is to manually or chemically irritate the site, causing a host immune response to achieve removal of the infected tissue. To prevent HPV infection of the lower anogenital tract from the most common high- and low-risk subtypes, the CDC recommends that boys and girls be vaccinated against HPV beginning at 11 to 12 years of age. It is also recommended that females be vaccinated up to age 26 and males up to age 21.

Anogenital and oropharyngeal warts can be managed similarly to cutaneous warts, provided the individual is immunocompetent. HPV-related carcinoma formation at these sites may require resection, chemotherapy and/or radiation. HPV-generated cervical lesions may resolve without any intervention. Young immunocompetent women with dysplasia are usually monitored at shorter intervals through Pap smears, HPV testing and colposcopic examinations. Persistent cervical dysplasia at any age, or high-grade dysplasia in older women, is managed with cryotherapy, loop electrosurgical excision procedure (LEEP) or cold-knife cone excision (CKC). Both surgical techniques (LEEP, CKC) involve resection of the cervical os and transformation site. If the individual progresses to malignancy, additional resection, chemotherapy and/or radiation may be required(2,12-14).

Differential Diagnosis

- Keratoacanthoma.
- Psoriasis.
- Corns and calluses.
- Herpes simplex.
- Molluscum contagiosum.
- Flat condyloma.
- Seborrhea.
- Chancroid.
- Acrochordon.

Prognosis

The prognosis following HPV infection is good, but recurrences are common. Although there are several treatments for warts, none work well and many of those affected require repeated treatments. HPV infection can also lead to vulvar intraepithelial dysplasia, cervical dysplasia and cervical cancer. Several women remain at high risk of developing vaginal and anal cancer. The risk of malignant transformation is higher in immunocompromised individuals. Also, when a person has been diagnosed with HPV infection, there is a 5-20% risk of having other STDs such as gonorrhea and/or chlamydia.
Cervical cancer screening with cytology has significantly reduced the incidence and mortality of cervical cancer in developed countries, although its sensitivity for detecting CIN2+ is around 66%(1).

Complications

Some complications may occur, such as:

- Progression to malignancy.
- Transmission of HPV to other individuals
- Genital warts can cause urethral obstruction.
- Condylomas can cause ulcers and become infected.
- Poor cosmesis.
- Depression.
- Decreased self-esteem.

Prevention

As part of prevention, the following recommendations should be considered:

- Avoid having multiple sexual partners.
- Practice safe sex, use a condom.
- Undergo a Pap test.
- Vaccination

The HPV 9 valent vaccine is available to prevent some cancerous lesions in men and women. The vaccine covers HPV subtypes 6, 11, 16, 18, 31, 33, 33, 45, 52 and 58, however the efficacy of the HPV vaccine against HPV has been inferred from multiple trials. It has been shown to prevent anal cancer, genital warts, cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia and anal intraepithelial neoplasia. The vaccine is most effective when given prior to the onset of sexual activity between 9 and 12 years of age. It is advisable to educate individuals that if they have HPV, they should be screened for other sexually transmitted infections. Screening of sexual partners is crucial to break the cycle of spread(2,15,16).

Once HPV is acquired, recurrences are common. However, for most individuals with genital warts, treatment is available. Approximately 60% of the time, genital warts resolve spontaneously. Regardless of the management of genital warts, the risk of cervical cancer is not altered. Of concern with genital warts is the risk of cervical cancer. HPV is associated with anal and head and neck cancers. Immunosuppressed individuals are also at risk of forming dysplasia or cancer of the vagina and vulva. Finally, in at least one third of individuals with HPV, there are other sexually transmitted infections(17,18).

CONCLUSIONS

It is of remarkable importance to know the human papillomavirus outlook, especially because it is linked to a number of underlying clinical manifestations of both benign, premalignant and malignant conditions. The authors recommend prevention, especially suggesting that boys and girls be vaccinated against HPV starting at 11 to 12 years of age, in addition to the other measures outlined in the article. It is important to understand that HPV alone does not cause cancer, but requires triggering factors such as smoking, folate deficiency, exposure to ultraviolet light, immunosuppression and pregnancy. Individuals with cutaneous warts have numerous treatment alternatives available, including surgical removal, cryotherapy, irritant or immunomodulatory medications, and laser removal.

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