

EDITORIAL

Human Papillomavirus in ENT - current state of knowledge

Vlad Andrei Budu^{1,2} , MD, PhD, Lecturer

¹"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

²Colentina Clinical Hospital, Bucharest, Romania



Human Papillomavirus (HPV) infection is caused by a DNA virus, which is part from the Papillomaviridae family. There have been described more than 170 types of HPV, many of them being responsive for cancer developing. The figures from the World Health Organization reveal that 15% of the population have current HPV infection, but an additional 60% have antibodies, which means that 75% of the population has been exposed to HPV infection. In most cases, HPV is transient and has no clinical manifestations. Unfortunately, in the late years there have been described low-risk subtypes of HPV (subtypes 6, 11) responsive for most of the HPV infections in ENT, but also high-risk oncogenic strains (subtypes 16, 18) mainly responsive for cervical cancer and squamous cell carcinoma of the oropharynx.

Why is it very important to understand the actual situation of HPV infection? Our concern regarding HPV infection and the risk of head and neck cancer developing has raised in the last decade, especially after we have seen in a prestigious journal of cancer the role of HPV infection in genital and non-genital cancers and the most interesting issue was the prediction of number of new cases in the next decade^{1,2}. What we have realized at the moment was the decreasing annual number of cervical cancer cases (due to vaccination) and the huge increasing number of oropharyngeal cancer (3 times more in 2030 than cervical cancer). The diminished number of oropharyngeal cancers in women (man:woman ratio = 7:1) is determined also by the good results of the HPV vaccination campaign.

Are there any particular features in HPV infection in ENT? In the ENT field, HPV infection has been found in all head and neck regions: mouth and oral cavity, tonsils and oropharynx, nasal cavity and sinuses

and larynx. The most common site of cancer due to HPV infection is the oropharynx. The immune system of some infected individuals may sometimes fail to control the HPV infection. If there are high risk HPV types (16, 18, 31, 45, etc.), the risk of cancer appearance is increasing. The development of cancer is caused by integrating the HPV genome into nuclear DNA. The early genes expressed by HPV (E6, E7) act as oncogenes and determine tumor growth and malignant transformation³. Other risk factors for head and neck cancer are smoking, alcohol abuse, radiations and other environmental factors.

What did we realize in the last years in ENT? First of all, we discovered an increasing number of HPV infections and a large prevalence of HPV in head and neck cancers (20-30% HPV in head and neck cancers). The HPV subtype 16 is present in more than 80% of head and neck cancers, the oropharynx being the most frequent anatomic site involved⁴. Head and neck cancers appear far more frequently in men than in women and has been proven that HPV infections in ENT are mainly sexually transmitted.

What is the main problem in HPV infection in ENT? Our up-to-date diagnosis protocols are based on clinical symptoms, endoscopic appearance, imagistic investigations, viral exam (tissue sample biopsy, DNA isolation, HPV genotyping test) and histological findings. The real problem for the ENT practitioner is the fact that we deal with the pathology when the tumor exists and has developed in head and neck anatomic sites, and treatment begins when papillomas appear in all anatomical sites of the head and neck region. The solution is for sure to find the proper ways to prevent HPV infections, beginning from an early age (preteens have a higher immune response to HPV vaccine than older teens). Vaccination for

girls and boys as well is the key factor in preventing the development of HPV-related cancers in ENT.

What is specific in every HPV-infected anatomic site in the head and neck region? In the oral cavity, HPV infections are mostly sexually transmitted and the prevalence of HPV infection is around 7% of the population. Usually, oral warts are not associated with cancer development and surgical removal can be easily performed. In oropharyngeal HPV infections, small papillomas can arise in the velum region or the tonsillar region and can be resected in a non-invasive approach. The most common HPV-related head and neck cancer (more than 70% prevalence) is located in the oropharynx and it is usually a squamous cell carcinoma⁴. Treatment can be unimodal or multimodal, depending on the cancer stage, and the results have not obviously improved in the last decades. So, in this particular cancer, we consider that prevention is the key for good results, but HPV vaccination is the solution. In the sinonasal pathology, HPV can be found in 60% of the cases in this specific type of tumor: the inverted papilloma⁵. This unilateral tumor has an aggressive growth and a high risk of recurrence (20-80% from the literature) and malignant transformation (10-30% in published articles)⁶. Depending on the tumor dimensions and the adjacent structures involved, surgical approach can be endoscopic or open technique. Laryngeal papillomatosis in children can cause respiratory dysfunction and it has a high grade of recurrence. Recurrence can be found also in adults, but the main problem of laryngeal papilloma is malignant transformation. HPV prevalence in laryngeal papillomas gets up to 70% and several therapeutic directions, surgical or antiviral, have been developed

Where do we stand with HPV infection in ENT? For the moment, our resources are really good concerning the diagnosis of HPV infections. We are quite capable of finding early symptoms of the disease, use all our endoscopic tools for examination, relay on the imagistic findings and establish a therapeutic approach. Surgery has become more complex using novel surgical tools (endoscopic sinus surgery, LASER surgery, robotic surgery), but treatment in HPV infection is, as mentioned, multimodal. Despite surgical treatment, therapy consists also of viral systemic therapy (Interferon, Ribavirin, etc.), intralesional injection (Cidofovir), topic appliance (Mitomycin C) or, still under study, antiangiogenic factors (Bevacizumab). The main problem consists in our capacity to implement all the prevention measures and especially HPV vaccination.

As a conclusion, our strategy is based on: prevention

of HPV infection, an early-stage diagnosis in HPV related tumors of the head and neck, using all the directions of the multimodal treatment, developing new clinical trials, involving mass-media structures for better understanding this important issue, but most of all providing a relentless campaign for HPV vaccination either for girls and boys at an early age (11-12 years old).

My last ideas go straight with the recommendations of the American Society of Clinical Oncology⁷, beginning with the question "If you could prevent cancer, would you?". As far as we know, HPV infection is preventable. HPV is passed from person to person during direct skin to skin contact, particularly during sexual activity. The Centers for Disease Control and Prevention recommends HPV vaccination⁴ for all boys and girls at age 11 or 12 years, all men through age 21, all women, gay or bisexual men and people with lowered immune system through age 26. Getting the HPV vaccine could save at least 7 out of 10 women from cervical cancer, 6 out of 10 men and women from oropharyngeal cancer, 9 out of 10 men and women from anal cancer, and the list is still open. So, prevention of HPV infection must be the first step in the management of head and neck cancers, and the solution is, undoubtedly, vaccination.

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