



## CLINICAL, EVOLUTIVE AND THERAPEUTIC ASPECTS OF RECURRENT RESPIRATORY PAPILOMATOSIS

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**Abstract.** HPV infection is one of the most common sexually transmitted diseases. The majority of infections cause no symptoms and are self limiting, being cleared without sequelae. Persistent infections are associated with various clinical aspects (cervical cancer, genitoanal warts, recurrent respiratory papillomatosis). Recurrent respiratory papillomatosis (RRP) is a rare but possible clinical outline. This article provides updates on the epidemiology, pathology, clinical and imaging features, treatment and evolution of RRP. Sexual education and HPV vaccines represent the most important tools against HPV infection.

**Keywords:** HPV infection, recurrent respiratory papillomatosis, child

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### General Data

The infection caused by the human papilloma virus (HPV) is the most common sexually transmitted infection in the US. The prevalence of HPV infection is the highest among young women aged 14-24. Estimating the exact prevalence and incidence is difficult because most of the HPV infections do not have a specific symptomatology and are self-limited (90% of the HPV infections are transient, with a benign evolution, self-limited within 1-2 years). Currently in the US, it is estimated that approximately 20 million persons are infected, that is 50-75% of sexually active persons, with an annual rate of 6.2 million new cases.

The risk factors for HPV infection are age (under 25 years old), number of sexual partners and the sexual history of the partners.

The persistence of HPV infection over time (approximately 20 years) is associated with dysplastic and neoplastic lesions localized mainly in the cervix (*cervical cancer, other anogenital cancers, genital warts, etc*).

In the world, 1400 women are diagnosed with cervical cancer every day, and 750 of them will die from it. Every year there are 500,000 new cases diagnosed globally and approximately 270,000 deaths occur because of cervical cancer. In other words, a woman dies from cervical cancer every 2 minutes.

In Romania, approximately 3500 women are diagnosed with cervical cancer every year and over 2000 die from it. Romania is ranked first in Europe for cervical cancer mortality, which is 6.3 times higher than the EU average.

There are over 100 types of HPV identified to date causing infections in humans. Some serotypes are associated with benign clinical manifestations (low-risk HPV), while others are associated with a severe clinical picture (high-risk HPV). Table I shows the main types of HPV and the clinical manifestations during the infection.

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Group	HPV Types	Manifestations
High-risk	Types 16, 18, 31, 33 and 45	Low-grade cervical changes High-grade cervical changes Cervical cancer
Low-risk	Types 6 and 11	Anogenital and other cancers Benign low-grade cervical changes Condylomata acuminata (genital warts) <b>Recurrent respiratory papillomatosis</b>

**Table I.** The most common HPV type associated with benign and malignant disease

The most common clinical aspects of the HPV infection are: genital warts, cervical cells abnormalities, anogenital squamous cell cancers, recurrent respiratory papillomatosis RRP.

Estimates of HPV-associated disease in the United States show that approximately 1% of the patients present with genital warts, 4% have colposcopic (subclinical) changes, 10% have no lesions, but are HPV DNA positive, 60% have no lesions or DNA, but have positive HPV antibodies. Some of these patients present with RRP (Urger E.R., 2001).

The HPV infection is most frequently transmitted through sexual contact (Kjaer SK, Chackerian B, 2001) – sexual contact, genital – genital contact, manual – genital contact, oral-genital contact, non-penetrative sexual contact. The infection can rarely be transmitted through a nonsexual route (vertical transmission) from mother to newborn (Smith EM, Ritchie JM, 2004). Recurrent respiratory papillomatosis in infants and children is the consequence of this kind of transmission.

## Recurrent respiratory papillomatosis

### General data

Recurrent respiratory papillomatosis (RRP), also known as laryngeal papillomatosis, is the most common benign neoplasm of the larynx among children, and the second most frequent cause of chronic childhood dysphonia (Derkey CS., 2001). In children, RRP presents with a severe clinical picture while in adults the symptomatology is more discrete. The age distribution of RRP is bimodal: the first peak occurs between ages 2-4 (childhood/juvenile-onset RRP), the second peak occurs between 20-40 years (adult-onset RRP). The incidence of juvenile-onset RRP is 0.75–4.3/100.000, while the incidence of adult-onset RRP is 1.8/100.000.

Table no. II shows data about incidence, demography, number of surgical interventions, as well as costs for treating persons with RRP, data from a study performed by Derkey CS and colleagues.

Cases in the US	Juvenile-onset RRP (diagnosis before the age of 12)	Adult-onset RRP (diagnosis after the age of 12)
Diagnosis age <sup>1</sup>	2-4 years	20-40 years
New cases/year <sup>2</sup>	2354	3623
Active	5970	9015
Surgical interventions/year <sup>2</sup>	16,597	9284
Annual costs <sup>2</sup>	109 million \$	42 millions \$

<sup>1</sup> Derkey CS. Laryngoscope 2001, 111:57-69

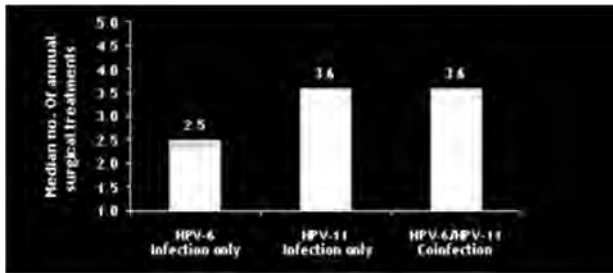
<sup>2</sup> Derkey CS. Arch. Otolaryngol Head Neck Surg. 1995, 121:1386-1391

**Table II.** The incidence and impact of RRP in children and young adults

In extremely rare cases, the infection can be iatrogenically transmitted (Kashima HK, Mounts P, 1998) through surgical gloves or instruments etc.

### Epidemiology

RRP is caused by HPV serotypes 6 and 11, also responsible for the anogenital condylomas. The HPV 11 infection is associated with a greater severity of RRP disease (fig. 1). HPV 11 or HPV 11/6



\*Statistically significant between HPV-11 single or coinfection and HPV 6 infection. Maloney EM. *Arch Otolaryngol Head Neck Surg.* 2006

**Figure 1.** A comparative study between the serotype of HPV infection and RRP severity

coinfection requires more surgical interventions, suggesting more severe manifestations of RRP.

HPV infection occurs at birth as the child passes through the birth canal. There is a 200-400-fold increased risk if the mother has an active anogenital condyloma at the time of delivery. High prevalence of condylomas caused by HPV and low prevalence of RRP mean there are other factors involved in developing the disease. It is estimated that there is a lower prevalence among babies delivered by cesarean section. Still, a woman's HPV status (presence or absence of HPV) does not solely constitute a C-section indication - *Derkay C.S., Urger E.R., Rimmel E., 2002.*

The juvenile-onset RRP is more aggressive than the adult-onset RRP (transmission through sexual contact), requiring repeated surgical procedures in order to maintain airway permeability. Still, the severity of RRP is independent of HPV viral load. The HPV viral loads for HPV 6 and 11 are also not associated with clinical severity indicators (*duration of illness, tracheal lesions, number of annual surgical procedures, number of months between treatments, age at diagnosis etc.*) - *Maloney E.M., 2006.* It must be noted that the immunodeficiency increases the severity of RRP.

The risk factors for this disease have been identified: first born babies, maternal genital condylomas at time of delivery, young mother, vaginal delivery, low socioeconomic status. There is a discrepancy between the incidence of the maternal genital infection (25%) and the rarity of RRP, the individual susceptibility thus playing an important role in the onset of the disease and in the future clinical picture.

### Anatomopathology

The recurrent respiratory papillomatosis is characterized by multiple papillomas located mainly in the airways (pharynx, larynx – most

frequently; trachea, bronchia, lung – *nodular lesions, pneumatoceles.*)

Histologically, papillomas are stratified squamous epithelial masses that can obstruct the airway if not removed (*Abramson AL, Nouri M, 2004.*) Though histologically benign, RRP causes significant morbidity and mortality due to the recurrent nature of the disease (*McClay JE, 2005.*) Papillomas have a similar histological structure both in children and in adults; the only differences are the recurrent character and the dramatic clinical picture of the disease in children. Furthermore, RRP may be a possible cause of head and/or neck cancers (*Szentirmay Z, Pólus K, Tamás L, et al. 2005.*)

Figure 2. shows one of the locations of RRP.



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**Figure 2.** Laryngeal Papillomatosis

### Clinical and imagistic aspects

RRP presents with varying clinical pictures depending on the location of the papillomas. As a general rule, the symptomatology is severe in cases with childhood-onset (before 3 years of age) because there are multiple localizations that determine important obstacles according to their size, necessitating frequent surgical interventions and, sometimes, even tracheotomy. The clinical symptoms and signs of RRP are: abnormal crying (at a young age), dysphonia, chronic laryngeal cough, inspiratory stridor, recurrent respiratory infections, sometimes even signs of acute respiratory distress/respiratory failure caused by upper airways' obstruction, suprasternal retractions.

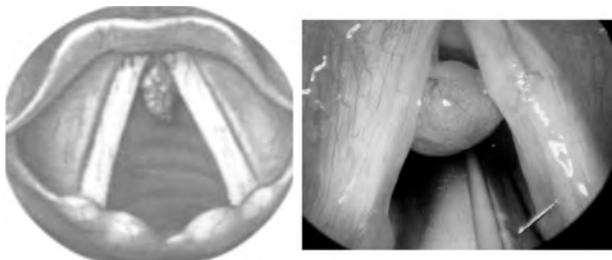
At the onset of symptomatology, it may be mistaken for other conditions (vocal cords nodules,

acute laryngitis, asthma, bronchitis). RRP is typically diagnosed between 2-4 years of age, with delay in diagnosis of 1 year after symptoms' onset.

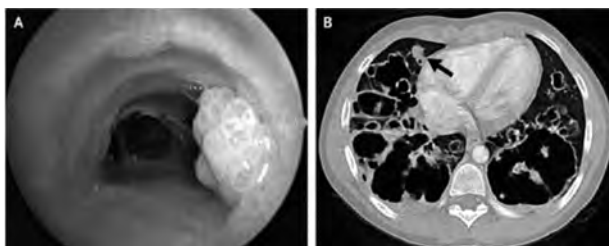
The persistence of the symptoms (dysphonia, persistent laryngeal cough) requires an airway endoscopy.



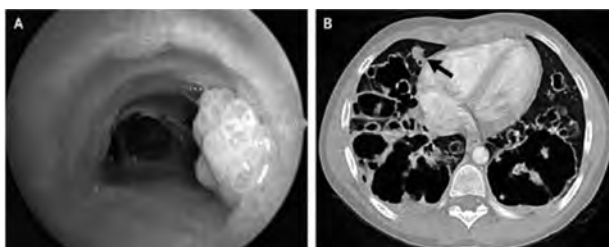
**Figure 3.** Papillomatosis located in the left nasal fossa



**Figure 4.** Laryngeal Papillomatosis (a, b) – located in the vocal cords



**Figure 5.** Laryngeal Papillomatosis with tracheal and subsequent pulmonary dissemination



**Figure 6.** Laryngeal Papillomatosis – radiologic and endoscopic image

Figures 3, 4, 5 and 6 show endoscopic aspects of recurrent respiratory papillomatosis.

### Treatment

The treatment of respiratory papillomatosis consists in surgical intervention and medical therapy.

### Surgical Therapy

Surgical/laser excision of papillomas is the most commonly employed removal method. Populational studies show that papillomas have a recurrent character; that is why it is estimated that during the first year after diagnosis, a patient usually requires 3-4 surgical procedures. Performing a tracheotomy must be carefully considered, especially in case of juvenile-onset RRP. This procedure has to be avoided whenever possible in order to prevent the spread of infection to the squamocolumnar junction and the emergence of new tumors distal to the initial lesions.

### Medical Treatment

Several medical therapies have been tried over time (cytostatic medicines, antiviral agents, immunosuppressive drugs, antibiotics etc.), as add-ons to the surgical therapy, but results were discouraging.

Some authors recommend Interferon  $\alpha$  as treatment, while others recommend antiviral agents (Cidofovir - cytosine nucleotide analogue) administered intralesionally (Bodaghi, S., Wood, LV., Roby, G., et al., 2005). The antiviral therapy induces apoptosis, amplifies the immune response leading to the regression of papillomas and to the reduction of the number of surgical interventions.

In 2007, a meta-analysis on the efficacy of the antiviral agents for RRP treatment led to recommendations specifying that the antiviral agents should only be routinely used as adjuvant therapy in those with moderate to severe RRP, not responding to surgery alone (Neil K. Chadha, MB ChB, et al., 2007).

### Outcome, Prognosis

The latency of HPV infection is the key to understanding this disease. The recurrences are due to focal activation of the virus and not to the actual spread of the condylomas from one location to another. All patients with HPV infection clinically expressed as RRP have very low levels of viral RNA or protein in the larynx for more than 20 years from the primary infection, though the infection

persists. Under these circumstances, the only way to cure RRP is to eliminate the latent virus.

The natural history of RRP consists in upper airways' obstruction which imposes repeated surgical excisions leading to remission or aggravation followed by tracheotomy.

In other cases, the infection may disseminate to the subsequent segments (trachea, bronchia, lung) or it may transform to malignancy in adolescents and young adults.

## Conclusions

HPV infection is one of the most common sexually transmitted diseases (50 - 75% of the sexually active population).

HPV infection is associated with varying clinical aspects (genital warts, cervical cells' abnormalities, anogenital squamous cell cancers, recurrent respiratory papillomatosis – RRP).

Sexual education and HPV vaccines represent the most important tools against HPV infection.

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