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JUVENILE LARYNGEAL PAPILLOMATOSIS: FROM ETIOLOGY TO TREATMENT

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ABSTRACT. The juvenile laryngeal papillomatosis is the most frequent benign tumour of the larynx. In 1800 Sir Morrel MacKenzie describes papillomas as pharyngo-laryngeal lesions at a child, and the term of juvenile laryngeal papillomatosis has been introduced by Chevalier Jakson in 1940. The etiological agent is HPV types 6 and 11 and the section of the respiratory tract the most frequently infected is the squamocolumelar junction. Juvenile laryngeal papillomatosis is a disease more frequent between 3 and 5 years, characterised by multiple relapses and exuberant growth at the level of the laryngeal mucosa. The annual costs of the treatment of this disease are over 123 million USD. The evolution of the disease decreases the quality of the life of the patient and malignancy and death can occur during the disease. *Objectives:* bringing new informations about the etiology, the diagnosis and the treatment of the disease for the specialties that deal with this pathology, especially paediatrics and otolaryngologists. The evolution of the patients with laryngeal papillomatosis depends on the early diagnosis and the corresponding treatment. *Material and method:* using data from the literature of specialty and the clinical experience in the ENT Clinic in Timisoara we present actualities in the epidemiology, the diagnosis and the treatment in the juvenile laryngeal papillomatosis. *Conclusions:* juvenile laryngeal papillomatosis is caused by the HPV types 6 and 11. The treatment of this disease isn't standardised; for this reason it is sometimes different for every patient depending on the formation of the specialist and the technology available in every clinic. The treatment follows two objectives: relapses and the reestablishment of the respiratory and phonatory function.

Keywords: juvenile papillomatosis, HPV, laser CO2, cidofovir, interferon

HISTORY

Juvenile laryngeal papillomatosis is a disease that develops at the level of the airways at all ages.

In 1800 Sir Morrel MacKenzie descibes papillomas as pharyngo-laryngeal lesions at a child, and the term of juvenile laryngeal papillomatosis has been introduced by Chevalier Jakson in 1940.

The juvenile form is more frequent between 3 and 5 years, but it doesn't disappear at teenagers and can also be founded in adults.

In the western countries it reaches 4-7 cases in a million persons (4 cases in 100,000 children, 2 cases in 100,000 adults). In the USA, to better understand this disease there have been taken a series of initiatives coordinated by the centers for the control and prevention of the diseases and by the American Academy of Pediatric Otolaryngology; they refer at data regarding the etiology, the epidemiology and the transmission of the laryngeal papillomatosis, the diagnosis and the individual treatment.

ETIOLOGY

Rontsky et al. estimate that 10-20% of the USA population aged between 15-45 years is infected with HPV and that 60% have been infected previously.

The etiologic agent is HPV types 6 and 11; the part of the respiratory tract the most frequently infected is the scuamocolumelar junction.

HPV is part of the Papovaviridae family. In the laryngeal papillomatosis the types the most frequently encountered are the types 6 and 11 at children and also at the adults.

The virions are of small sizes (45-55nm), spherical, without envelope. The genome is a double-strained DNA, circular and spiral. The genome encodes proteins that stimulate cell proliferation which can cause either cell lysis (in permissive cells), either neoplasic transformation (in nonpermissive cells).

HPV presents tropism for squamous epithelial tissue, skin and mucosa; at this level the virus replicates and induces cell proliferation generating tumoral entities.

Papillomas develop preferably in the anatomic regions of transformation, where the squamous epithelium meets ciliated columelar epithelium. To produce a long lasting disease it is necessary that the genome persists during cell division. The papilloma virus possesses three features responsible for occurrence of the papillomatosis:

1. The viral reproduction which allows the dissemination of the papillomas, the alteration of the cellular growth and the persistence of the virus at the level of the respiratory mucosa;

2. The persistence and the replication of the episomal genome (in undifferentiated status) needs the presence of two early genes E1 and E2; this type of replication takes place in the undifferentiated basal cells, but only a part of this episomal mechanism of auto-persistence has been elucidated;

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3. The viral gene E2 binds the viral genome to the chromosomal DNA of the host in such a way that it can be retained and kept during mitosis. When the keratinocyte differentiation takes place the viral genome is amplified in parabasal cells continuously, processes that furnish enough viral genome to be enveloped. This change in the amplification of the viral genome dependent of the differentiation has been correlated to the late expression of the E1-E4 genes after an isoform head to head model. This way it has been emitted the hypothesis that cell differentiation activates the production of these late genes, this way allowing the assembly of the virus.

The mechanisms of the replication, the persistence and the viral production of the types 6 and 11 in the cells of the respiratory tract are mainly unknown, and currently there are known only the mechanisms of the types 16 and 31. The perturbance of the cell growth is generated by the presence of the genes E6 and E7. These proteins bind and alterate the function of two apoptotic key-proteins Rb and p53. This mechanism refers to the type 16 with the most increased virulence. Until now this mechanism has not been proved also in types 6 and 11.

The presence of the types 6 and 11 at the level of the respiratory mucosa is not enough to produce the growth of the papillomas is not enough to produce the growth of the papillomas and the alteration of the cell growth. Of the two viruses the most aggressive is the type 11, which can cause malignant degeneration.

Many authors showed that the virus can remain in a latent status and only in the presence of particular factors cellular alteration can occur, factors that currently are not entirely known. The pathway for the transmission of the HPV virus is proved to be direct during vaginal birth at patients infected with papilloma virus or with condiloma accuminata, during birth by caesarian section or by contaminated objects and surfaces, in uterus by infected sperm, ascendant infection trough the genital tract, transplacentar or sexually (numerous partners, oral sex).

Currently we do not know the factors that cause the occurrence of the juvenile laryngeal papillomatosis only in a part of the infected persons with HPV types 6 and 11. Data from the literature show that the number of persons infected with these types is greater than the one of those who developed laryngeal papillomatosis. Current research tries to show what are the factors and the mechanisms that underly to the occurrence of this disease.

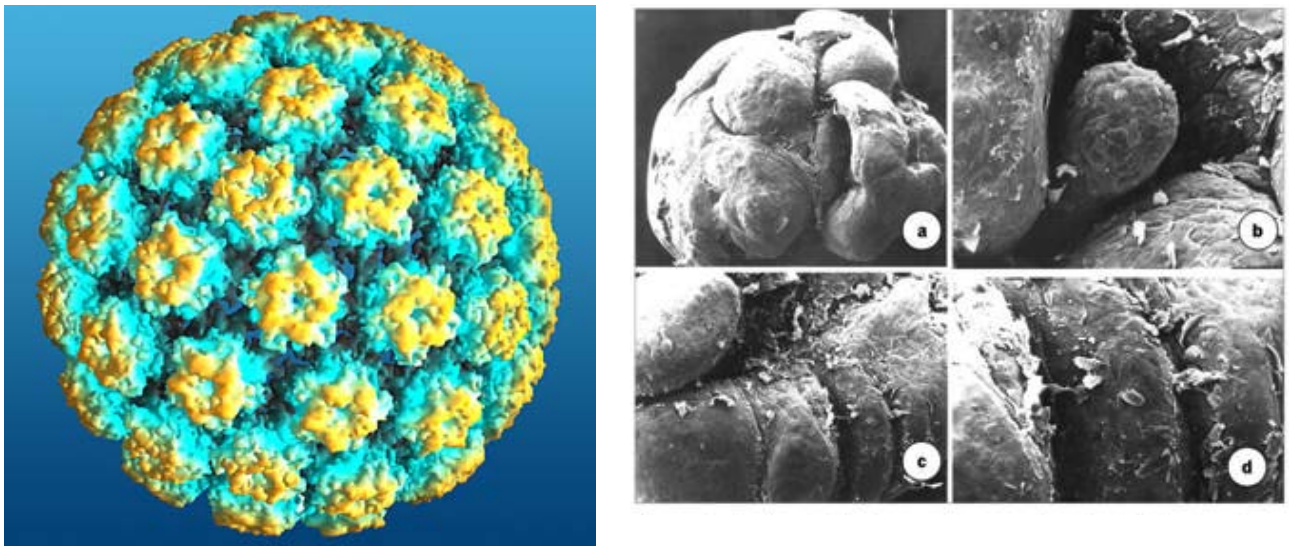

Fig. 1, 2 Surface of the laryngeal mucosa involved by type 6 HPV (scanning electron microscopy a-x50, b-x1000, c-x2500, d-x200)

The clinical forms of the laryngeal papillomatosis are according to age: the juvenile laryngeal papillomatosis and the papillomatosis of the adult.

The localization of the lesions

The classic localization for the recurrent disease in the aero-digestive tract is: the soft palate, limen vestibuli, the middle part of the epiglottis (the laryngeal surface), the superior and inferior edges of the ventricle, the inferior surface of the vocal folds (anterior and middle thirds), the carina, the bronchi, the trachea, the lungs and the esophagus.

The diagnosis is based on the history, the subjective symptoms, the clinical exam, the histopathological exam through suspended laryngoscopy, techniques for the detection of the HPV.

The symptomatology is characterized by the progressive disphonia generally after an infection of the upper airways, progressive dispneea, odinofagia, globus or dysphagia. The ENT clinical exam is made by indirect laryngoscopy, fibroscopy or suspended laryngoscopy. This examination can show the presence of diffuse tumoral growths cauliflower-like, reddish due to the vascularisation more abundant, generally

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situated at the level of the vocal folds, the ventricles, the endolaryngeal surface of the epiglottis, the subglottic region and sometimes the trachea.

We can also present a classification of the papillomas according the localization:

- Degree 0 - without lesion;
- Degree 1 - one lesion on one of the vocal folds;
- Degree 2 - less than 3 lesions on one or both the vocal folds;
- Degree 3 - 3 or more lesions on one of the vocal folds;
- Degree 4 - 3 or more lesions on both the vocal folds;
- Degree 5 - 3 or more lesions on both the vocal folds accompanied by extraglottic lesions.

The histopathological examination is very important in the diagnosis of this disease and is characterized by the presence of connective-vasculary axis (papillae) that represent the stroma of the tumor, covered by squamous epithelium tumorally proliferated, thickened, with regular stratification, without obvious cellular abnormalities, generally without mitotic activity or with typical rare mitosis. Typical changes for the HPV infection are para- and diskeratosis and koilocytosis (intracellular vacuolization). Rarely there can be observed epithelial dysplasia and even malignant transformation.

The techniques applied for the analysis of the HPV are: immunohystochemical dyes, DNA hybridization sensitive for the detection of the viral DNA and the typing of the HPV and the PCR which shows a high incidence of the HPV DNA in the papillomatosis of the adult and child detecting HPV in 85-100% of the cases.

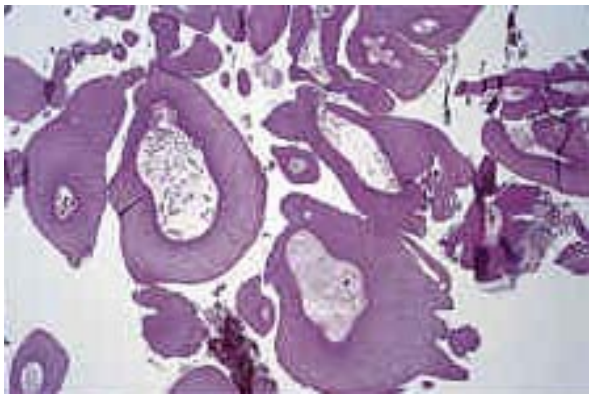

Fig. 3 Juvenile laryngeal papillomatosis, histological aspect

The differential diagnosis is made with the polyp of the vocal fold, the Reinke oedema, the nodules of the vocal folds, the subglottic laryngitis, the leukoplakia, the laryngeal hemangioma and even laryngeal cancer.

The evolution and the prognosis are according the principal feature of the juvenile laryngeal papillomatosis, the capacity to relapse, which cases a significant morbidity in the ENT pathology. The malignant transformation is another feature, but very seldom encountered.

The cases of malignant transformation are encountered in children and also in adults in the infection with HPV 6 and 11. the most frequently it is encountered in the infection with HPV 11, when the malignant transformation is associated with the integration of HPV 11 in the genome and the mutation of p53, and the factors that favor the malignancy are external, physical and chemical (radiation, tobacco, alcohol). The clinical criteria that suggest the malignant transformation are: the dysphagia, the rapid and exuberant growth of the papillomas that make the surgical intervention necessary at less than 2 months to maintain the airway, the subglottic extension, laryngeal oedema especially in the supraglottis that causes obstruction of the airway even after the complete removal of the papillomas, the need for tracheotomy to maintain the airway, the limitation of the mobility of the vocal fold and the cervical adenopathy.

TREATMENT

There have been used numerous therapeutically methods worldwide with the purpose to prevent or limit the number of the relapses, to keep the airway and the phonatory function of the larynx. This treatment has two steps: the surgical treatment and the adjuvant therapy. Currently there is no standard treatment; it is realized according the experience of the ENT practitioner and the equipments of the service in which the patient is treated.

The surgical treatment refers to the classic surgery (ablation of the papillomas with the forceps trough suspended laryngoscopy), debrider surgery, laser surgery, cryotherapy and photodynamic therapy.

The adjuvant therapy that is realized currently is not standard, and worldwide it is most frequently done with α2 interferon, indol-3-carbinol and cidofovir.

The surgical treatment the most frequently used worldwide is the ablation of the papillomas with the debrider, which has the advantage to better keep the phonatory function at a lower cost. The laser surgery makes reference at argon and laser CO_2 surgery that acts on tissues without causing their burst, and the energy produced by the beam converts in heat in the tissues, vaporizes intracellular water and melts the tissues leaving a relatively superficial carbonized crater. The wound healing after laser ablation is excellent. The Nd-Yag laser resection is the therapy the most effective, but has inconvenient like: rigid bronchoscopy, expensive equipment, adequate training and can generate very severe complications. This type of laser has also antiviral features.

Adjuvant therapy is necessary when the patient needs more than 4 surgical resections in one year, for multifocal dissemination and when the fast growth of the papillomas compromises the airway permeability. The α2 interferon is the mostly used treatment, modulating the immune response with an increased production of the proteinkinase and the endonuclease

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that inhibits the viral protein synthesis. It is administrated in dose of 100,000 UI/kg/day, 5 days in a week, for 11 months, followed by 50,000 UI/kg/day, 5 days in a week, for 1 month. In case of relapse the histopathological examination is mandatory, and the therapy can be repeated.

The side effects are characterized by: acute reactions (fever, chills, choriza, headache, mialgia), chronic reactions (growth delay, transaminase increase, leucopenia, fever convulsions). There have also been described thrombocytopenia, rash, dry skin, alopecia, generalized itchiness and fatigue. This is why the patients at which interferon is administrated must be investigated before treatment and supervised during the therapy. The interferon produced by recombination has fewer side effects.

Cidofovir is an antiviral agent recently approved by the FDA for the treatment of the patients with HIV and citomegalic chorioretinitis; it is a nucleoside analogue. In the treatment of the laryngeal papillomatosis it is administrated trough intralesional shots and the dose used is of 1mg/kg in 4 sessions, at 2 weeks interval between sessions. There have been reported administrations of 5mg/kg i.v., but these can generate acute renal failure, that restored after the interruption of the therapy. Literature describes the occurrence of malignant tumors after the administration of cidofovir (adenocarcinoma).

Mandatory criteria necessary for cidofovir therapy are: histopathological confirmation of the squamous papillomas of the larynx, minimum 4/year ablation surgical interventions, patient older than 6 months. Lab tests before therapy initiation include: complete blood tests, serum creatinin, electrolytes and liver tests. All these tests are repeated between 1-4 months after the first dose. On the other hand, there are exclusion criteria like: concomitant chemotherapy in the last 2 months, concomitant nefrotoxic medication, history of malignancy, renal diseases, radiotherapy on respiratory tract, positive pregnancy test, positive HIV test, serum creatinin greater than 1mg/dl, hematocrit < 30%, leucocytes < 4,000/ml, serum urea greater than 25 mg/dl or modification of any of the tested values.

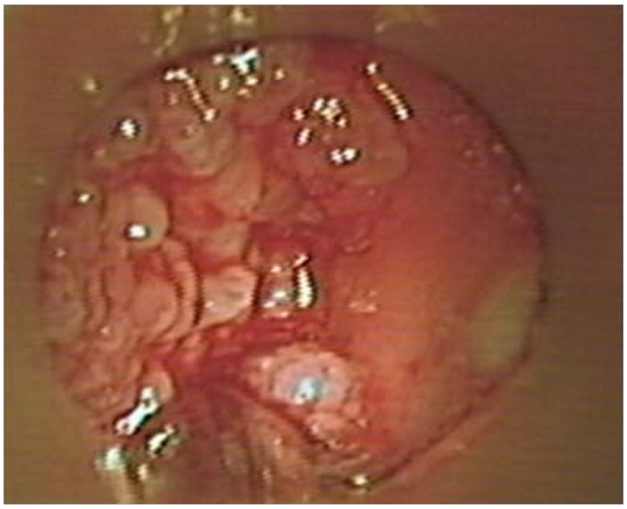

Fig. 4 Female 4 years old with juvenile laryngeal papillomatosis before treatment

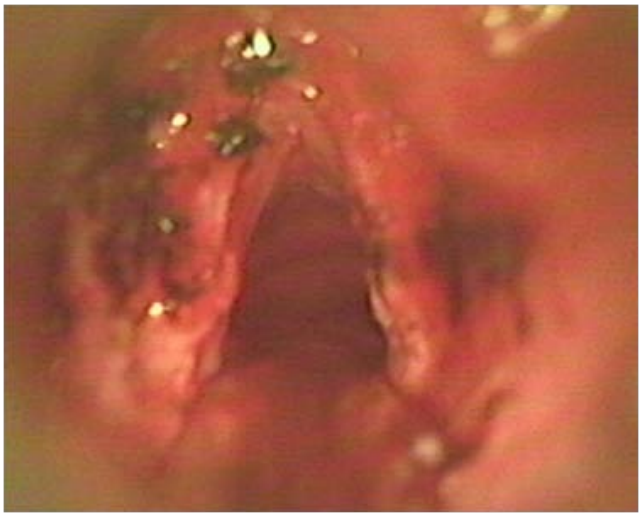

Fig. 5 Female 4 years old with juvenile laryngeal papillomatosis after treatment with laser CO_2

CONCLUSIONS

Juvenile laryngeal papillomatosis is a benign disease with low incidence, but with extraordinary morbidity and for this reason, even now it can cause problems regarding evolution and treatment. There are two major objectives for the specialists: relapses and maintenance of the phonatory function. Currently we know a lot of information about the HPV, but not enough about the types 6 and 11, responsible for the occurrence of the laryngeal papillomatosis. Current data cannot explain why a part of the infected patients develop the disease, and others don't. The only method to solve the two objectives is the early diagnosis and the surgical and adjuvant treatment. The experience of the ENT Clinic in Timisoara is based on the ablation of the papillomas with laser CO_2 and the therapy with α2 interferon.

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