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Recurrent Respiratory Papillomatosis: A Review

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Abstract

Recurrent Respiratory Papillomatosis (RRP) is a disease of exophytic lesions in respiratory epithelium and vocal folds, being an important cause of childhood dysphonia. The etiology comes from the *Human papillomavirus* (HPV) which presents the host with high morbidity, in addition to being a precursor to neoplasms such as squamous cell carcinoma. The disease is more severe in its juvenile form, while in the adult form the disease occurs less frequently. Clinically it is pathology of nonspecific symptoms. The diagnosis is confirmed by laryngoscopy and the treatment has as principles the control of the disease and keeping the patient's airway clear, since there is no cure until the present moment. Although surgery is the main form of disease control, adjuvant treatments with cidofovir and bevacizumab have shown a better prognosis for the disease. The HPV vaccine has also been related to therapeutic and prophylactic effects, resulting in a decrease in the number of procedures per year.

Keywords: Recurrent respiratory papillomatosis; HPV; Cidofovir; Bevacizumab

Introduction

Recurrent Respiratory Papillomatosis (RRP) is a disease characterized by proliferative exophytic lesions in the respiratory epithelium and vocal folds. It is the most prevalent benign neoplasm of the larynx in children and the second most frequent cause of childhood organic dysphonia. The cause of the disease is an infection by *Human papillomavirus* (HPV), a DNA virus that penetrates the host system through micro abrasions [1]. Even with a low incidence, ranging from 0.5 to 4.0 per 100,000 inhabitants, *HPV* has great morbidity and recurrence, causing severe functional consequences, beyond social and financial loss over patient's life [2].

In most cases, RRP presents itself as multiple lesions that affect the supraglottis, the commissure and the anterior third of the vocal folds. The first symptoms present in patients with changes in vocal quality, dyspnea, stridor, cough or recurrent respiratory infections [3].

Types 6 and 11 are responsible for more than 90% of RRP cases [2,4], while types 16 and 18 are considered high-risk ones and can suffer potentially malignant transformation, particularly in squamous cell carcinoma [5,6].

RRP shows a characteristic of bimodal distribution, affecting children and young adults. The juvenile form develops most of the time in patients under 12 years of age and is generally more aggressive, with multiple papillomatous lesions with a high rate of recurrence [7]. The adult form usually develops between 20 and 40 years of age, more commonly in men [8]. In this second form, papillomas are often solitary and recur in a less frequently way than those seen in the juvenile form [5].

The clinical course of RRP is unequal and spontaneous remission, persistent infection or malignancy may occur. It is not clear yet why the disease has different outcomes [9]. RRP usually presents with nonspecific symptoms of airway involvement, including chronic cough, dysphonia, stridor and dyspnea. The diagnosis in the child takes one year on average to be confirmed due to misdiagnoses such as asthma, bronchitis, laryngitis and laryngomalacia. The diagnosis of laryngeal papilloma is made through rigid or flexible laryngoscopy. In children, the exam can be comfortably performed under sedation [10].

There is currently no known cure for RRP as no treatment eliminates the virus from laryngeal tissues. The goals of treatment are to keep the airway free; to improve and preserve the voice; to avoid tracheostomy and, as far as possible, to control the disease. Surgery is still the main pillar in

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the treatment, using cold microsurgery, laser or microdebrider [4]. The objective of surgery is to remove the maximum of the disease without damaging adjacent structures, preventing complications that can occur such as glottic stenosis [1].

About 20% of patients with RRP require adjuvant medical treatment in addition to surgery to control the disease. The current criteria for adjuvant therapy are more than four annual surgical procedures, rapid recurrence of papillomas with airway involvement and distal dissemination [1,11].

Cidofovir, a cytosine analog, is currently the most commonly used antiviral in medical adjuvant treatment for RRP. Several studies conclude that the adjunctive intralesional administration of cidofovir can lead to partial to total regression of the lesions and a reduction in the frequency of surgical procedures. The use of cidofovir is off label. Recommendations are for a maximum dose of 40 mg/kg in adults and 3 mg/kg in children [12,13].

Bevacizumab is a monoclonal antibody developed using the recombinant DNA technique. Local intralesional injection has been used in RRP with some success. Systemic bevacizumab as a treatment for RRP has shown some dramatic successes in particularly severe cases, refractory to other medical treatments [1]. The recommended dose ranges from 5 mg/kg to 10 mg/kg of intravenous infusion with an intermission of 3 weeks [14,15].

HPV vaccines have been available since 2006 in the United States (USA) and Europe and have been accepted with great interest ever since [16]. The tetravalent vaccine (types 6, 11, 16 and 18) has a good global distribution. Recently, the nonavalent vaccine was launched with coverage for types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

Studies in populations with at least 10 years of vaccine implantation have shown pronounced decreases in *HPV*-related diseases [17,18]. In an Australian study, a decline in the annual RRP incidence was observed from 0.16 to 0.02 per 100,000 children [19].

Since 2009, it has been hypothesized that HPV vaccination could have a therapeutic effect on PL, preventing the formation of papillomas in new locations [20], since the immune response triggered by the vaccine is more robust than that caused by HPV infection [21]. Several studies have been published indicating the therapeutic effects of the vaccine in patients previously infected with HPV with a decrease in the number of procedures/year [22].

Although RRP is a benign disease, it has high morbidity due to the involvement of the airway and frequent recurrences. No treatment guarantees a cure even with all the therapeutic methods employed. The advancement of surgical techniques for treatment, associated with adjuvant therapies, such as cidofovir and bevacizumab, has shown a better prognosis for the disease. The vaccine seems to be great hope in protecting future generations [8].

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