

# *Adjuvant therapy for laryngeal papillomatosis*

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## **K E Y W O R D S**

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## **A B S T R A C T**

Respiratory papillomatosis affects the larynx in most cases. It is a relatively rare disease, with potentially devastating consequences for the patient. Many studies have proven the viral etiology of the disease. Surgery is the most successful mode of treatment. Adjuvant therapy is used in cases of aggressive disease. The most successful adjuvant drugs are interferon, various virostatics (e.g., acyclovir, valacyclovir, and cidofovir) and indole-3-carbinol. Vaccination with a quadrivalent vaccine against HPV will probably decrease the incidence of respiratory papillomatosis or help in the treatment of the disease in the future. The results of adjuvant therapy of laryngeal papillomatosis at the University Department of ORL & HNS in Ljubljana are comparable to the results in other centers around the world.

## **Introduction**

Respiratory papillomatosis (RP), which most often affects the larynx, is a relatively rare benign disease that can, however, have an aggressive clinical course (1, 2). The age distribution of patients has two peaks: the first is at an age of less than 5 years and the second in the 20-to-40 age bracket (3, 4). In the U.S., the incidence of the disease is assessed at approximately 1.7 to 4.3/100,000 children, or 1.8/100,000 adults (5, 6).

Lindeberg et al. proposed a classification of the disease into juvenile and adult forms in relation to the first appearance of the disease (3). In terms of the clinical course of the disease, a classification into “aggressive” and “non-aggressive” forms is more appro-

priate. The term “aggressive form of the disease” is used when a total of more than 10 surgical procedures, or more than three procedures annually, are required in order to improve the patient’s condition (7).

Human papilloma virus (HPV) has been found in the great majority of patients with RP. More than 120 different types have already been found, although RP is most often caused by types 6 and 11 (5, 8). Experts presume that infection most often occurs in children upon birth or even during gestation. Two possibilities of infection exist in patients in whom the disease appears in adulthood: either infection occurred during birth and the outbreak of the disease only appeared later because of a breakdown of the immune system

(deficiency of cell immunity), or infection occurred later through oral or sexual contact (e.g., oral sexual contact) (4–6, 9–12).

Both children and adults most often seek medical help because of increasing hoarseness. With growth of the papillomas, breathing difficulties and stridor occur, which fortunately rarely require tracheotomy (1, 3, 5, 12). In rare cases, the papillomas also spread to the lower respiratory tract, a development normally associated with a poor prognosis (6). Even more rarely (in 3 to 7%) the papillomas undergo malignant changes (5, 9, 12). On the other hand, individual cases have also been known in which the papillomas spontaneously regress, which could be connected with hormonal or immunological changes in the patient (5, 7, 10, 12, 13).

Approximately equal proportions of patients with juvenile and adult forms of the disease have an aggressive course (17% and 19%, respectively) (6). Some factors associated with an aggressive disease course have been established: infection with HPV 11, early spread of the disease to the subglottis, appearance of the disease before age 3, gastroesophageal reflux, and concurrent infection with other viruses (5, 10, 12–14).

The basic mode of treatment of RP is still surgery under general anesthesia. During the operation, the surgeon attempts to remove as many of the papillomas as possible in order to improve the respiratory path and the quality of voice. At the same time, it is desirable to have as little damage to the mucous membranes and other structures in the larynx as possible, so as not to induce scarring. The CO<sub>2</sub> laser has been the most successful tool in surgical treatment for a number of years and recently a “microdebrider” has been increasingly used. The likelihood of the formation of scars in the larynx increases with the number of operations. Dye lasers have also been successful in the treatment of RP because of their angiolytic effect on the blood vessels in the papillomas (5, 10, 12, 13, 15).

Adjuvant therapy is required in 10% of patients with the aggressive form of the disease. Twenty years ago, interferon was most commonly used but it has a number of adverse effects (16). Virostatics (e.g., acyclovir, valacyclovir, and cidofovir) are also used as adjuvant drugs and act on HPV as well as other viruses. Indole-3 carbinol and its metabolites influence the metabolism of estrogen and thus decrease the growth of the papillomas (10, 12, 17–21). It has been found in clinical trials that, after treatment of gastroesophageal reflux in children with RP, the number of recurrences is significantly reduced. The authors therefore recommend treatment of reflux mainly in patients with an aggressive form of the disease (22, 23). Quadrivalent vaccination against HPV, which has been shown to be successful in preventing HPV genital infections, also

protects against infection with HPV 6 and 11. With wider use of vaccination in the future, a reduction in the incidence of RP may also perhaps be expected in both juvenile and adult forms (12).

The purpose of our research was to establish how successful adjuvant therapy was in patients treated at the University Department of Otorhinolaryngology and Cervicofacial Surgery (ORL & CFS) in the last 32 years.

## Patients and methods

Among the patients treated at the ORL & CFS Department in Ljubljana between 1979 and 2011, we identified patients with an aggressive form of the disease in terms of the criteria proposed by Doyle (7). We extracted data from the medical documentation on the extent of the disease according to the Derkay et al. protocol (24), the method of treatment, and the periods between individual surgical operations. In all patients treated after 2001, we determined the level of antibodies to herpes simplex virus (HSV 1, HSV 2), cytomegalovirus (CMV), and Epstein Barr virus (EBV) in order to decide whether to treat with acyclovir or valacyclovir. In patients in whom the disease course was aggressive and that were treated with adjuvant therapy, we compared the periods between individual operations before and after the start of the adjuvant therapy. We followed the patients for 7 to 103 months after the start of adjuvant therapy. We considered treatment to have been completely successful if, after completing treatment, a maximum of one operation was required and the papillomas did not subsequently reappear throughout the follow-up period. Partial success meant that, after the end of the treatment, the intervals between surgical procedures were at least twice as long as before the treatment. If the growth of the papillomas did not slow by at least 50%, we considered the treatment to have been unsuccessful.

## Results

From 1979 to 2011, 182 patients (125 males, 57 females) were treated at the ORL & CFS Department. In 31 patients (14 boys, 17 girls) the disease appeared before age 15, and in the others it appeared during adulthood. Patients' ages at the time of diagnosis ranged from 9 months to 82 years.

All patients were treated surgically. Until 1996, papillomas were removed microsurgically. Later operations took place with the aid of a CO<sub>2</sub> laser, but the papillomas were still excised microsurgically during the initial procedure. In one-third of patients the disease appeared only once, whereas the others required

from 2 to 43 surgical procedures, with an average of 2.3 operations per patient.

RP had an aggressive course in 27 patients (15 males, 12 females) ranging in age from 5 months to 53 years at the first appearance of symptoms, and from 9 months to 53 years at the time of diagnosis of the disease. After 1999 all patients with an aggressive form of the disease were treated with proton-pump inhibitors, specifically with esomeprazole, omeprazole, or pantoprazole at a standard dose twice daily until improvement (defined as slower growth of papillomas).

When there was a finding of HSV 1 or HSV 2 infection, as was the case in 14 patients (12 adults, two children) with the aggressive form of the disease, the patients were treated with acyclovir or valacyclovir at a standard dose for 2 months. The extent of the disease and time periods between individual surgical procedures are shown in Table 1.

Five children with the aggressive form of the disease received indole-3 carbinol for 6 months to 3 years. The interval between required surgical procedures doubled and in three children growth of the papillomas ceased after 2 years of taking the medication (Tables 1 and 2).

In the cases of nine individuals (one child, eight adults) we decided to inject cidofovir into the site of the papillomas following laser ablation, in a concentration ranging from 2.5 to 7.5 mg/ml. The patients were injected with the drug from one to nine times and received a total dose of 10 mg to 75 mg. In the juvenile patient, after nine injections of cidofovir with a total dose of 26.25 mg the papillomas stopped growing and did not reappear in the following 2 years of follow-up (Tables 1 and 2).

We decided on vaccination with three doses of quadrivalent vaccine (HPV 6, 11, 16, 18) in individuals with the aggressive form of the disease or very quickly growing papillomas, and above all in patients not helped by other adjuvant treatments. We vaccinated seven adults and one child (six females and two males). The results of treatment at the end of the follow-up period are shown in Tables 1 and 2.

Nine patients that experienced lack of success with one of the adjuvant drugs were further treated with another adjuvant drug or received a vaccination, and two patients were vaccinated after the failure of two adjuvant drugs.

*Table 1. Comparison of the extent of respiratory papillomatosis, interval between surgical procedures, and number of surgical procedures before and after adjuvant therapy.*

Adjuvant drug	Extent of disease		Interval between procedures (months)		Procedures (n)	
	Before	After	Before	After	Before	After
Acyclovir/valacyclovir	7.2	7.1	6.5	8.8	9.1	3.3
Indole-3 carbinol	9.9	10.4	3.5	7.4	7.6	6.3
Cidofovir	7.2	7.2	4.6	2.8	5.6	3.4
HPV vaccination	7.6	4.9	6.5	16.7	14.8	1.6

*Table 2. Review of success of treatment with different adjuvant drugs in patients with aggressive forms of respiratory papillomatosis.*

Adjuvant drug	Patients (n)	Follow-up time (months)	Complete response	Partial response	Not successful
Acyclovir/valacyclovir	14	17–103	7	4	3
Indole-3 carbinol	5	48–84	1	2	2
Cidofovir	9	7–22	1	7	1
HPV vaccination	8	24–32	2	4	2

## Discussion

RP is a rare disease, affecting a small number of patients, and so statistical evaluation of success does not have real value. In this paper, which summarizes the results of adjuvant therapy in 27 patients with aggressive RP, we decided to present our results without statistical evaluation.

Estimates of the extent of papillomas before and after adjuvant therapy did not differ greatly, which is evidence that we always decided on surgical intervention when patients were in relatively the same clinical condition. The extent of the papillomas reduced by a good third after vaccination alone. The number of operations before and after adjuvant therapy is also difficult to compare because the time before the start of adjuvant therapy was essentially longer than after it. The group of patients with an aggressive form of RP included four patients that underwent from 10 to 38 operations before adjuvant therapy, for an average of 22.5 operations, which undoubtedly also influenced the average number of operations before adjuvant therapy.

A better method of evaluating the success of treatment is determination of the interval between individual surgical procedures before and after adjuvant therapy, or an overall clinical evaluation of the success, which covers the extent of the disease, speed of growth of the papillomas, and number of operations required (that is, complete or partial response to therapy or lack of success). In terms of this evaluation, in summary we found a complete response to therapy in 31%, partial response in 47% and, in the case of 22% of patients, adjuvant therapy was unsuccessful.

According to data from the few studies available, acyclovir or valacyclovir have been used successfully as adjuvant therapy after surgical removal of papillomas in 50% of cases (21). These data could confirm the significance of concurrent infection with other viruses during the course of RP, mainly infection with HSV. The success of our patients' therapy with this virostatic is similar to that described in the literature because we recorded complete success of adjuvant therapy in half of the patients. Only those patients with the aggressive form of the disease in whom simultaneous infection with HSV 1 or HSV2 was confirmed were given the drug.

In recent years there have been some reports of the use of cidofovir (10, 12, 17, 18). Cidofovir is an analogue of the cytosine nucleotide, which is built into the DNA chain of the virus. It is most commonly injected directly into the larynx at the site of the papillomas after their prior surgical removal in very ag-

gressive forms of the disease. In patients whose lower respiratory tracts are affected, cidofovir is given also systemically. The success of cidofovir in the treatment of RP was even greater than 60% (10, 12, 17–19). In our patients, we observed partial or complete success in eight of nine patients treated. We also injected the drug only locally at the site of the papillomas. We achieved the greatest success in a 2-year-old girl, in whom an operation was required practically every 2 months because of the fast growth of the RP. After 9 injections of cidofovir, the papillomas stopped growing. In 2009, a warning was issued that cidofovir could increase the survival of cells and induce changes in gene expression, which is known to be connected with malignant transformation in cells (25). In view of these data and the drug manufacturer's requirement that cidofovir now be used exclusively for CMV infection of the eyes, we stopped using cidofovir.

Indole-3 carbinol affects estrogen metabolism and redirects it into a metabolite that decreases the growth of papillomas. We have used the drug in children with partial or complete success in 75% of cases (22). The success of treatment in our patients was comparable with success worldwide.

Since establishing the success of vaccination against HPV for preventing uterine cancer, vaccination has been recommended for girls 11 to 12 years old, or also women up to age 26, and in some countries even for boys. Because quadrivalent vaccination also protects against infection with HPV 6 and 11, a reduction of the incidence of RP with more widespread vaccination in the future can probably be expected (12). Individual reports of the success of the use of quadrivalent HPV vaccine for the treatment of RP have also been published (26, 27). We decided on vaccination in patients with the most aggressive course of the disease or those in whom one or even two adjuvant drugs had not been successful. The course of the disease improved in 6 of 8 vaccinated patients. Only with further follow-up will the exact role of vaccination against HPV in the treatment of RP be proved.

## Conclusion

Respiratory papillomatosis is a relatively rare disease of the upper respiratory tract with possible devastating consequences for the patient in some cases. In aggressive forms of the disease adjuvant therapy is used. It is necessary to consider carefully which drug to use in order to achieve the best possible results. This is the best way to bring about improvement in the condition and thus the quality of life of patients with respiratory papillomatosis.

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