

THE USE OF COMBINED TREATMENT WITH CO₂ LASER MICROSURGERY AND INTERFERON ALPHA 2B IN JUVENILE RECURRENT LARYNGEAL PAPILLOMATOSIS

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REZUMAT

Obiective: Papilomatoza laringiană juvenilă (PLJ) este o afecțiune de etiologie virală caracterizată prin multiple recidive ale formațiunilor tumorale benigne ale mucoasei laringiene, care determină o morbiditate semnificativă în patologia pediatrică ORL. Scopul studiului este de a evalua rezultatele tratamentului combinat prin microchirurgie endoscopică cu laser CO₂ și Interferon alfa 2b la copiii cu papilomatoză laringiană. **Material și metodă:** Între 1996-2004, 23 pacienți cu vârste cuprinse între 2,9-8 ani, au fost diagnosticați cu papilomatoză laringiană. Tratamentul a constat în microchirurgie endoscopică cu laser CO₂, urmată de tratament adjuvant cu Interferon alfa 2b. S-a practicat excizia și vaporizarea formațiunilor tumorale, sub anestezie generală, cu o bună expunere a zonei operatorii. Traheotomia nu s-a practicat la nici un caz. **Rezultate:** Examinările endoscopice postoperatorii au constatat regresia formațiunilor papilomatoase la toți pacienții. La 16 pacienți s-a constatat regresia completă a afecțiunii, după microchirurgia cu laser CO₂, ca metodă primară, și tratamentul adjuvant cu Interferon. Răspunsul parțial la tratamentul combinat s-a constatat la 7 pacienți. În aceste cazuri a fost necesară reintervenția. Nu s-au înregistrat complicații intraoperatorii și postoperatorii, precum și efecte adverse severe ale tratamentului cu Interferon. **Concluzii:** Tratamentul combinat al papilomatozei laringiene reprezintă terapia de elecție, cu perioade de remisiune lungi. Acest tratament a îmbunătățit prognosticul acestei afecțiuni virale. Rezultatele funcționale bune, cu controlul local al formațiunilor tumorale papilomatoase, spitalizarea de scurtă durată, reprezintă elementele favorabile ale acestei metode de tratament la copiii cu papilomatoză laringiană.

Cuvinte cheie: papilomatoză laringiană juvenilă, tratament cu laser CO₂, tratament cu Interferon alfa 2B

ABSTRACT

Objective: Juvenile recurrent laryngeal papillomatosis (RLP) is a viral disease characterized by multiple recurrences of benign tumours of the larynx mucosa and significant morbidity on paediatric patient and strain on their families. The aim of this study was to evaluate the results of combined treatment with CO₂ laser microsurgery and interferon (IFN) alpha 2b in children suffering from laryngeal papillomatosis. **Material and method:** During a 10 years period (1996-2004) 23 patients aged from 2.9 to 8 years diagnosed with laryngeal papillomatosis were included in the study. Case management consisted of CO₂ laser microsurgery followed by adjuvant therapy with IFN. All patients underwent microsurgical excision and progressive vaporization of papillomas with the CO₂ laser under general anaesthesia and good exposure. Tracheotomy was not necessary in any of the cases. **Results:** Clinical examination revealed regression of papillomas in all patients. 16 patients had complete regression after primary CO₂ laser microsurgery and additional interferon treatment. 7 patients had partial response to the combined treatment. In these cases second intervention was needed. No perioperative or postoperative complications and no severe side-effects were noted. **Conclusions:** This combined treatment is a method of choice in laryngeal papillomatosis in children, causing longer remission of the disease. Surgical ablation with laser CO₂ is the elective treatment and its combination with IFN improved the prognosis of this recurrent viral disease. Reachable functional results, good tumour control, short hospitalization makes it a favourable treatment in paediatric patients.

Key Words: juvenile laryngeal papillomatosis, CO₂ laser treatment, IFN alpha 2B

INTRODUCTION

The scientific understanding of juvenile recurrent laryngeal papillomatosis (RLP) has been a slow process. In 1871, MacKenzie noted the frequent association of

skin warts and laryngeal papillomas. Ullmann in 1923 was the first to verify an infectious etiology by injecting homogenized papillomata from a child's larynx into his own forearm and observing the development of papillomata there.¹ However, it was not until 1956 that a paediatrician made an association between maternal condylomata and the risk of childhood infection.² In 1973 an intranuclear icosahedral virus was identified in lesions by electron microscopy, and in 1980 human papillomavirus (HPV) DNA was identified in papillomata.^{3,4} Surgical debulking was advanced with the use of the CO₂ laser and suspension microlaryngoscopy in 1972, which remains the state of the art.⁵ Current areas of promise include the use of

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drugs to slow the disease progression. Originally called juvenile laryngeal papillomatosis, the disease has been increasingly recognized in adults and generally goes by the name recurrent respiratory papillomatosis (RRP).

The human papilloma virus (HPV) has more than 60 subtypes identified; 20 of these subtypes affect the epithelium of the genital tract. Condylomata acuminata (subtypes 6 and 11) and cervical dysplasia (subtypes 16, 18, 31, 33 and 35) are the most common clinical manifestations of HPV infections.⁶⁻⁸

The human papillomavirus is a naked, double-stranded, icosahedrally-shaped virus with circular supercoiled DNA that belongs to the Papovavirus family. "Papova" is an acronym for the three types of viruses in the family – papillomavirus, polyomavirus, and simian vacuolating virus. There are only three papovaviruses pathogenic to humans: HPV, JC and BK viruses which are polyoma viruses (JC virus has been implicated in progressive multifocal leukoencephalopathy and BK virus has been isolated from urine of kidney transplant recipients).

Juvenile recurrent laryngeal papillomatosis (RLP) is extremely aggressive and resistant to treatment, usually surgical.^{9,10} It typically involves the trachea, but may spread to the oesophagus and bronchi, and rarely, to the lung where it actually destroys tissue, dramatically worsening the prognosis. Although rare, it is the most common benign tumour of the larynx.¹¹⁻¹³

The incidence of RLP has been reported as 1:1500 live births.

RLP has a bimodal age distribution and presents most commonly in children younger than 8 years (juvenile-onset recurrent respiratory papillomatosis [JORRP]) or in persons in the fourth decade of life (adult-onset recurrent respiratory papillomatosis [AORRP]).

JORRP is more common and more severe than AORRP.

MATERIALS AND METHOD

Between 1.01.1996 - 31.12.2004, 23 patients with juvenile recurrent laryngeal papillomatosis (RLP) have been treated in the ENT Department Timișoara.

The mean age at diagnosis was 4.7 years. The proportion of juvenile recurrent laryngeal papillomatosis cases diagnosed between 2.9 and 3.9 years old was 13.04% (3 cases), from 4 to 4.9 years old 65.21% (15 cases), from 5 to 5.9 years old 8.69% (2 cases), respectively from 6 to 8 years old 13.04% (3 cases).

The juvenile recurrent laryngeal papillomatosis

(RLP) affects males and females in approximately equal number: 12 cases (52.17%) were females, and 11 males (48.83%).

The most common presentation of RLP was hoarseness - 22 cases (95.65%), voice changes occurred in 1 case (4.34%), young children also presented weak cry - 11 cases (47.82%), choking episodes - 9 cases (39.13%), foreign body sensation in the throat - 18 cases (78.26%), chronic cough - 15 cases (65.21%), dyspnea - 11 cases (47,82%), inspiratory wheezes in 20 cases (86.95%), and stridor in 13 cases (56.52%).

The diagnosis was made upon the visualization of warty excrescences and confirmed by biopsy. Histological there was an epithelial projection with a fibrovascular core, and there is associated parakeratosis, koilocytosis, and acanthosis.

For this study, the information was extracted from the ENT Department Timișoara database: age at RLP diagnosis; year of birth, symptoms. Patients were classified as JORRP if their age at diagnosis (approximation for age of onset of disease) was no more than 8 years.

Regarding localisation of the papillomas 18 cases (78.26%) presented papillomas at the level of vocal cords, and anterior commissure, 2 cases (8.69%) at the level of vocal cords and subglottic region and 3 cases (13.04%) at the level of vocal cords, anterior and posterior commissure, ventricular folds and laryngeal surface of the epiglottis. The localisation is due to temperature and moisture changes which facilitate the viral replication and proliferation. (Figures 1-4)

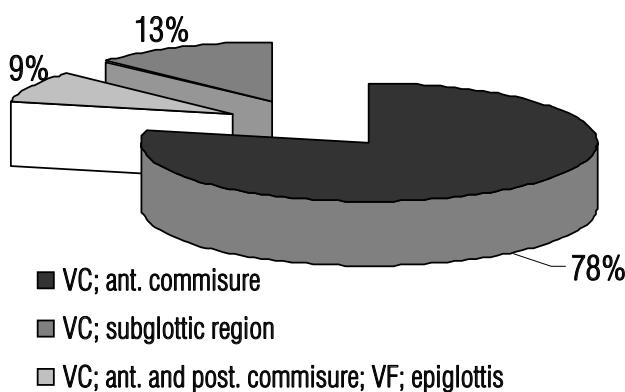


Figure 1. Papillomas localisation.

Case management consisted of CO₂ laser microsurgery followed by adjuvant therapy with IFN alpha 2b. All patients underwent microsurgical excision and progressive vaporization of papillomas with the CO₂ laser under general anaesthesia with good exposure of the anterior and posterior commissure. It was very important to preserve the anterior commissure in order to prevent anterior stenoses, which are not rare.



Figure 2. Intraoperative view.



Figure 3. Intraoperative view.

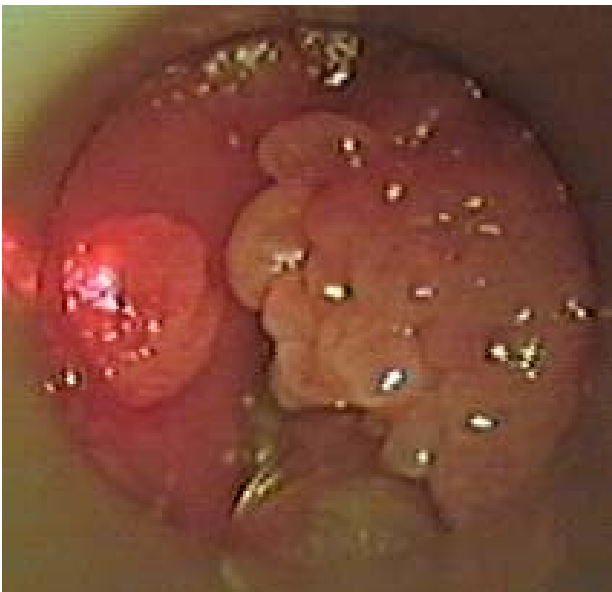


Figure 4. Intraoperative view.

Tracheotomy was not necessary in any of the cases. The dosage of IFN alpha 2b was 100,000 IU/kg/day, 5/7 days during a period of 11 month followed by 50,000 IU/kg/day, 5/7 days for 1 month. Functional aim was to preserve a functional glottis and to protect the laryngeal fundamental functions, for increased quality of patient's life. Followed-up period varied between 4 and 48 month (average 14 month). Follow-up data were available for all patients. All were followed up using a precise postoperative protocol.

RESULTS

One goal is to eradicate disease without damaging normal structures. Traditionally this has been done with either cold steel or with the CO₂ laser. Other goals of therapy are to relieve airway obstruction, improve voice quality, and facilitate remission. The primary treatment involves repeated surgical debulking usually by means of a carbon dioxide laser. When the papillomas formations were disseminated on a large surface and small in dimension (18 cases - 78.26%) localised at the level of vocal cords and anterior commissure, each formation was vaporised with CO₂ laser, taking care to not involve the vocal cord mucosa. It was used a continuous mode, 12-15 W or pulse mode at 0.1 seconds to avoid heating and coagulation. There was no bleeding. In case of large and obstructive papillomas formations (3 cases - 13.04% at the level of vocal cords, anterior and posterior commissure, ventricular folds and laryngeal surface of the epiglottis), we used a forceps, without touching the mucosa or free edge of vocal cord. The papillomas were excised using continuous mode. For restant tumours was used CO₂ laser in a pulse mode (0.1 second). Regarding posterior commissure and subglottic area (2 cases - 8.69%), the papillomas vaporisation was performed without intubation tube. This area is vaporised last, under a good haemostasis. (Figures 5-7)

Compared to laser procedures, surgical resection may be associated with a higher risk of complications (e.g, tracheal stenosis).

Due to its highest efficiency the CO₂ laser can be used in continuous, pulse and superpulse mode. Radiant wave of 10600 nm it is ideal for surgery, because it is absorbed by liquids and solids, it's not spread from the emergent beam, and the absorption is independent by the tissue colour. It does not create genetic mutations, it destroys cells by hyperthermia.

Treatment involves repeated debulking of the warty growths by laser surgery.

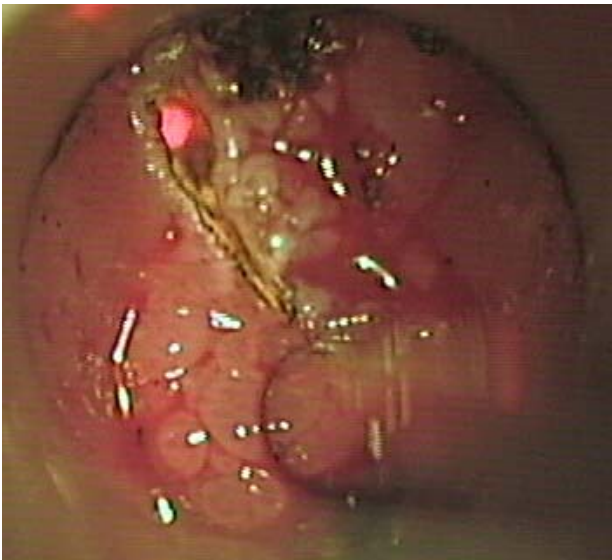


Figure 5. Intraoperative view.

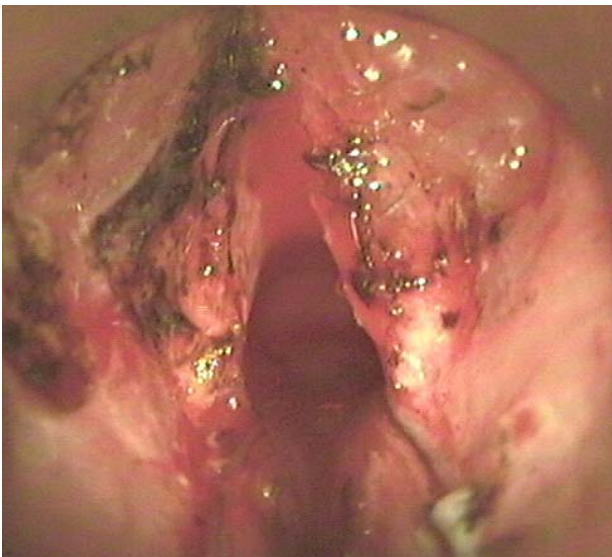


Figure 6. Postoperative view.

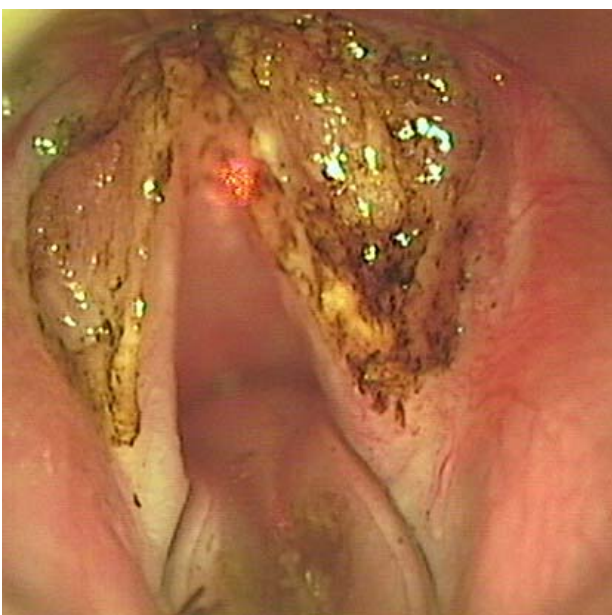


Figure 7. Postoperative view.

Care must be taken especially around the anterior and posterior commissures to avoid the formation of webs. It is better to be more conservative on one side and leave behind disease than to be aggressive and develop a web.

Care must be taken with the laser to avoid disastrous complications such as airway fire. Care must be taken to protect the operating room personnel as papillomata have been demonstrated in the laser plume. Good suction of smoke and laser operating masks are usually sufficient. Eye protection must be used to avoid laser damage to the globe.

Interferon is a product of human leukocytes, although it is now produced via recombinant technology. Interferon treatment appears to slow the rate of growth without curing the disease. Although some antiviral agents (e.g., cidofovir, acyclovir) also may slow the rate of regrowth of lesions, they are not curative. Eventually, some patients may enter remission.

Side effects include flu-like symptoms, elevation of hepatic enzymes, renal insufficiency, anorexia, seizures, GI distress, and transient numbness. There is some suggestion that neutralizing antibodies may blunt its beneficial effect and that this may vary by brand. Results may vary considerably from patient to patient.

The surgical interventions were performed under general endotracheal anaesthesia, concerned about the anesthesiological safety aspects of laser surgery. We didn't notice any accidents or complications regarding CO₂ laser procedures during these interventions.

No intra and postoperative haemorrhages occurred.

We used a minimal postoperative aftercare: antibiotic prophylaxis for 5 days with Ampicillin 2 g per day i.m. to prevent a bronchopneumonia or a local infection; mucolytics; minor antalgics in the first 24-48 hours to prevent local pain.

We have no postoperative complication. None of the 23 patients had impairment of voice. Clinical examination revealed regression of papillomas in all patients.

Functional results were very good at 22 patients (95.65%) and good at 1 patient (4.34%). The results of these 23 patients are:

- Free of disease in 16 cases, 69.56%;
- Seven patients had partial response to the combined treatment, in these cases second intervention was needed. Seven recurrences (30.43%) represented by 4 cases (57.14% out of 7 cases, 17.39% out of 23 cases) with one recurrence (at the age of 3.5 years, 4

years, 4.5 years and 4.8 years, respectively) and 3 cases (42.85% out of 7 cases, 13.04% out of 23 cases) with more than one recurrence (at the age of 2.9 years (2 recurrences), 4.5 years (3 recurrences) and 5.8 years (2 recurrences)). No perioperative or postoperative complications and no severe side-effects were noted.

Time interval from surgical intervention to recurrences was on the average 12 months, between 3 and 28 months. In cases of recurrence, the patient underwent CO₂ laser removal of the papillomas formations and adjuvant therapy with IFN alpha 2b.

Average hospitalisation was 5 days, between 3 days to 12 days for the patient with bronchopulmonar complication. Treatment failures, recurrences are due to its normal evolution of the disease.

DISCUSSIONS

Since the introduction of the endoscopic CO₂ laser microsurgery into clinical otolaryngological procedures, laser surgery for RLP has been gaining increasing importance. RLP represent the most common larynx benign tumour.

The typical course is of recurrent lesions requiring frequent debulking. However, every patient is different and treatment must be tailored to the individual. Some people require such frequent debulking that tracheotomy is necessary for airway protection. This unfortunately frequently leads to lesions around the tracheotomy site (in essence, an iatrogenic squamociliary junction), but traditional thinking has been that this predisposes to distal tracheal disease. A recent study of children, however, suggests that those who require tracheotomy have more aggressive disease and have distal disease prior to tracheotomy, and thus recommends that no child be subjected to a tenuous airway merely to avoid tracheotomy.¹⁴

Tracheotomy has two inconveniences: it facilitates the spread of papillomas and produces moisture changes which also facilitate the spread of the virus.

Interestingly, the virus can be detected in the normal mucosa adjacent to lesions. It is thought that this provides a reservoir for regeneration of new papillomata.¹⁵

The natural history of the disease includes spontaneous remission. It is impossible to know to whom or when this will occur. The causes of remission are not known, and while the exact incidence is not known, it is thought that approximately one-third will remit by age forty. This makes clinical trials somewhat difficult inasmuch as it confounds the ability to tell who remitted due to treatment and who remitted due

to the natural history of the illness. Usually a patient who requires multiple procedures develops a regular interval at which time he or she returns for elective debulking. This interval can be quite variable and depends on the patient.

A recent survey of otolaryngologists showed that 92% favoured the laser.¹⁶ The KTP laser can be used for more distal disease.

Management of the airway is controversial. In the apnoea technique the patient is intubated and administered 100% oxygen for a period of time. The tube is then removed for a period of time while the surgeon works. The patient is then reintubated and reoxygenated. This may be advantageous in paediatric airways in which there are not much room to work around a tube. Other methods include use of a laser-safe tube and spontaneous ventilation. Another common method is jet ventilation. Although this is generally felt to be safe, there is concern that this method may lead to distal inoculation of the virus. In patients with an existing tracheotomy, a metal tracheotomy tube can be placed to allow laser surgery to be carried out safely. A recent survey of otolaryngologists found the percent who favoured the various techniques as follows: laser-safe tube 46%, jet ventilation 25%, apnoeic 16%, and spontaneous 12%.¹⁶

Due to the nature of the disease adjunctive measures and alternative treatments have been sought out. In the absence of an effective antiviral agent, use of drugs that will augment host defence is a reasonable approach. Seventy-five to 80% of patients respond to interferon, with a complete response in about 30%. Interferon does not eradicate the virus, and relapse may occur after discontinuation of treatment. Therapies which have been explored but rejected include steroids, estrogens, cryotherapy, cautery, ultrasound, radiation, vaccines, resin of podophyllum, transfer factor, levamisole, suction diathermy, lymphokines, escarotics, calandine, magnesium, and antibiotics.¹⁷ Newer therapies which have been tested include alfa-interferon, indole-3-carbinol, acyclovir, retinoic acid, ribavirin, methotrexate, cidofovir, and photodynamic therapy.

Case reports suggest that combined treatment with acyclovir or retinoic acid may be beneficial in patients with recurrent disease during interferon treatment.

Some studies and uncontrolled observation in patients with RRP indicate that a diet high in cruciferous vegetables (egg, cabbage, cauliflower, broccoli, Brussels sprouts) may have a favourable effect. Researchers hypothesize that indole 3-carbinol is the active agent in these vegetables; its role is under study.

Cidofovir (Forvade[®], Vistide[®]) is currently approved for treatment of CMV retinitis in AIDS. Cidofovir is the first member of a group of antivirals known as acyclic phosphonate nucleotide analogs. In infected cells, nucleotide analogs such as cidofovir inhibit viral DNA polymerase, which is responsible for replication of new viral RNA and DNA. Because HPV is the causal agent for RRP, eradication of the virus offers the potential for cure. Intralesional use is beneficial.

The etiologic link between maternal condyloma at delivery and JORRP in the infant was first recognized by Hajek in a case report in 1956.² This observation was supported by additional case reports and by the finding that more than 50% of mothers of JORRP cases gave a history of having condylomas during pregnancy and/or at delivery.^{4,18,19} Subsequent virologic studies fully substantiated the link between genital condylomas and JORRP. HPV types 6 and 11 which are responsible for 80-90% of the condylomas are documented in nearly 100% of JORRP.²⁰⁻²² Transmission of the virus from mother to infant is believed to occur predominantly intrapartum, as the foetus passes through an infected birth canal.¹⁸ Cases of JORRP rarely give a history of caesarean birth, an indication that caesarean delivery decreases the risk of acquiring JORRP.²³ Adult-onset RRP (AORRP) is also caused by infection with HPV-6 and HPV-11 but very probably, the infection is not acquired at birth.²⁴

Genital tract infection with HPV-6 and HPV-11 is common, but JORRP is rare. Data are not available to make a reliable estimate of the risk of transmission from an infected mother to a child but this risk is perceived to be low.^{23,24}

The guideline on perinatal care of the American College of Obstetricians and Gynaecologists states that "caesarean delivery is not recommended solely to protect the neonate from HPV infection". We have estimated that the risk of transmission of JORRP from a condylomatous mother to an infant may be 1-3%, and could be as high as 8% for first-born children of teenage mothers (Bishai et al., unpublished data).²⁵ The assumptions on which these estimates are made, as well as other considerations (e.g., maternal morbidity due to caesarean delivery, cost-benefit analysis of caesarean delivery), need to be debated before a population-wide policy regarding the prevention of JORRP by caesarean deliveries is instituted, but personal choice is a different matter. It is highly probable that some women at risk would be willing to personally incur the extra expense and operative risk of caesarean delivery to eliminate a 1-8% chance of JORRP in their childhood. Several new approaches toward prevention

and treatment of condylomas are promising.^{26,27} Any treatment that would reduce the HPV viral burden in the genital tract during labour, or diminish fetal contact with maternal virus, would likely decrease the incidence of JORRP.^{28,29}

Caesarean delivery has been proposed as a potential means of preventing JLP. However, although caesarean delivery is rare among infants and children with JLP, HPV DNA has been found in amniotic fluid before rupture of the fetal membranes and in oropharyngeal swabs of infants born by caesarean section. It is also unclear whether, as with genital HSV, recurrent lesions are less likely than primary ones to result in maternal-fetal transmission. The protective potential to the foetus/neonate of caesarean delivery probably does not exceed its potential morbidity to the mother.

CONCLUSIONS

In conclusion, RRP is a disease which causes a substantial human and financial cost to the public. HPV has been shown to be the aetiology. It affects people of all ages. Life-threatening airway obstruction may develop. The natural history is poorly understood but is characterized by spontaneous remission in some patients. Treatment is essentially palliative with surgical debulking. Various adjunctive drugs have been developed which slow but do not eradicate the progression of disease in some patients. Currently there is ongoing research aimed at improving the treatment of this insidious disease.

Because the disease is uncommon and requires direct laryngoscopy for diagnosis, children usually have symptoms for a year before a physician makes the diagnosis. The morbidity of this disease has been studied more completely for JORRP, in which the average number of surgical procedures required is 4.4 per child per year, and the average number of procedures per child's lifetime is more than 20.

Although they can be found anywhere in the aerodigestive tract, there appears to be a predilection for areas where there is a junction of squamous and ciliary epithelium. This includes the limen vestibuli (junction of the nasal vestibule and the nasal cavity proper), nasopharyngeal surface of the soft palate, midzone of the laryngeal surface of the epiglottis, upper and lower margins of the ventricle, undersurface of the vocal folds, and the carina and bronchial spurs.

Because the disease is rare, large-scale trials of medical therapies have not been possible; however, several agents are available that appear to increase the intervals at which surgical debulking is

required. These include systemic and intralesional interferon, intralesional cidofovir, indole 3-carbinol, and photodynamic therapy. Agents that demonstrate variable effects include cimetidine, acyclovir, and retinoic acid.

The carbon dioxide laser is the preferred method for resection of papillomas because it affords good haemostasis and minimizes potential thermal injury of surrounding healthy tissues.

Combined treatment with Endoscopic CO₂ laser microsurgery and Interferon alpha 2 b is considered to be the election method in RLP, offering long remission periods and sometimes healing. CO₂ laser ablation permits the protection of vocal cords, allowing a normal breathing, and especially a normal voice. The associated treatment with IFN alpha 2b has largely improved the prognosis of this viral disease. The good functional results, with the local control of the tumour for a long period of time and a short hospitalization represent the most important advantages of this treatment method.

This combined treatment is a method of choice in laryngeal papillomatosis in children, causing longer remission of the disease. Surgical ablation with laser CO₂ is the elective treatment and its combination with IFN improved the prognosis of this recurrent viral disease. Reachable functional results, good tumour control, short hospitalization makes it a favourable treatment in paediatric patients.

REFERENCES

- Ullmann EV. On the aetiology of the laryngeal papilloma. *Acta Otolaryngologica* 1923;V:317.
- Hajek EF. Contribution to the etiology of laryngeal papilloma in children. *J Laryng Otol* 1956;70:166.
- Boyle WF, Riggs JF, Oshiro LS, et al. Electron microscopic identification of papova virus in laryngeal papilloma. *Laryngoscope* 1973;83:1102.
- Quick CA, Watts SL, Krzyzek RA, et al. Relationship between condylomata and laryngeal papillomata. *Ann Otol Rhin Laryng* 1980;89:467.
- Strong SM, Jako GJ. Laser surgery in the larynx: clinical early experience with continuous CO₂ laser. *Ann Otol Rhin Laryng* 1972;81:791-8.
- Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol* 2005;32(1):16-24.
- De Villiers EM, Fauquet C, Broker TR, et al. Classification of papillomaviruses. *Virology* 2004;324(1):17-27.
- Molijn A, Kleter B, Quint W, et al. Molecular diagnosis of human papillomavirus (HPV) infections. *J Clin Virol* 2005;32(1):43-51.
- Silverman DA, Pitman MJ. Current diagnostic and management trends for recurrent respiratory papillomatosis. *Curr Opin Otolaryng Head Neck Surg* 2004;121:532-7.
- Kenneth A. Diagnosis and management of human papillomavirus infections. *Ped Inf Dis J* 2005;24(11):1007-8.
- Sinal SH, Woods CR. Human papillomavirus infections of the genital and respiratory tracts in young children. *Sem Ped Inf Dis* 2005;16(4):306-16.
- Derkay CS. Recurrent respiratory papillomatosis. *Laryngoscope* 2001;111:57-69.
- Abeer M, Flanagan E, Lennox J, et al. Severe recurrent respiratory papillomatosis in an HIV-infected adult on highly active antiretroviral therapy. *J Bronch* 2005;12(4):210-3.
- Shapiro AM, Rimell FL, Pou A, et al. Tracheotomy in children with juvenile-onset recurrent respiratory papillomatosis: the children's hospital of Pittsburgh experience. *Ann Otol Rhin Laryng* 1996;105:1-5.
- Murray LN, Miller RH. Recurrent respiratory papillomatosis. *J Louisiana St Med Soc* 1998;150(10):456-9.
- Derkay CS. Task force on recurrent respiratory papillomatosis. *Arch Otolaryng Head Neck Surg* 1995;121:1386-91.
- Bauman NM, Smith RJ. Recurrent respiratory papillomatosis. *Ped Clin North Am* 1996;43(6):1385-401.
- Kaufman RS, Balogh K. Verrucas and juvenile laryngeal papilloma. *Arch Otolaryngol Otol* 1969;89:748-9.
- Cook TA, Brunschwig JP, Butel JS, et al. Laryngeal papilloma: Etiologic and therapeutic considerations. *Ann Otol Rhinol Laryngol* 1973;82:649-55.
- Gissmann L, Diehl V, Schultz-Loulou HJ, et al. Molecular cloning and characterization of human papillomavirus DNA derived from a laryngeal papilloma. *J Virol* 1982;44:393-400.
- Mounts P, Shah KV, Kashima H. Viral etiology of juvenile- and adult-onset squamous papilloma of the larynx. *Proc Natl Acad Sci USA* 1982;79:5425-9.
- Abramson AL, Steinberg BM, Winkler B. Laryngeal Papillomatosis: Clinical, histopathologic and molecular studies. *Laryngoscope* 1987;97:678-85.
- Shah K, Kashima H, Polk BF, et al. Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. *Obst Gynecol* 1986; 68:795-9.
- Kashima H, Shah F, Lyles A, et al. A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis. *Laryngoscope* 1992;102:9-13.
- Shah KV, Kashima H. Prevention of juvenile-onset recurrent respiratory papillomas. *Curr Opin Otolaryngol Head Neck Surg* 1997;5:107-11.
- Buetner KR, Ferenczy A. Therapeutic approaches to genital warts. *Am J Med* 1997;102:28-37.
- Baker GE, Tying SK. Therapeutic approaches to papillomavirus infections. *Dermatol Clin* 1997;15:331-40.
- Pasquale K, Wiatrak B, Woolley A, et al. Microdebrider versus CO₂ laser removal of recurrent respiratory papillomas: a prospective analysis. *Laryngoscope* 2003;113(1):139-43.
- Kahn J, Bernstein D. Human papillomavirus vaccines. *Ped Inf Dis J* 2003;22(5):443-5.