

RRP Medical Reference Service

An RRP Foundation Publication

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Preface

The *RRP Medical Reference Service* is intended to be of potential interest to RRP patients/families seeking treatment, practitioners providing care, micro biological researchers as well as others interested in developing a comprehensive understanding of recurrent respiratory papillomatosis.

This issue focuses on a selection of references with abstracts from recent (2011 and later) RRP related publications. These listings are sorted in approximate reverse chronological order as indicated by the "PMID" numbers. Each listing is formatted as follows:

Journal or reference
Title
Language (if it is not specified assume article is in English)
Author(s)
Primary affiliation (when specified)
Abstract
PMID (PubMed ID)

If copies of complete articles are desired, many journals do provide online access (some are free others do charge). You can also request a reprint from one of the authors. If you need assistance in this regard or if you have any other questions or comments please feel free to contact:

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RRPF Selected Articles and Abstracts

Int J Head Neck Surg. 2010 May;1(2):69-77.

Consistent DNA hypermethylation patterns in laryngeal papillomas.

Stephen JK, Chen KM, Shah V, Schweitzer VG, Gardner G, Benninger MS, Worsham MJ.

Source

Department of Otolaryngology-Head and Neck Surgery and Research Division, Henry Ford Hospital, Detroit, MI 48202.

Abstract

INTRODUCTION:

This study examined the contribution of promoter hypermethylation to the pathogenesis of respiratory papillomatosis (RP), including recurrences (RRP) and progression to squamous cell carcinoma (SSC).

MATERIALS AND METHODS:

A retrospective cohort of 25 laryngeal papilloma cases included 21 RRP, two of which progressed to SCC. Aberrant methylation status was determined using the multi-gene (22 tumor suppressor genes) methylation-specific multiplex ligation-dependent probe amplification assay and confirmed using methylation specific PCR.

RESULTS:

Twenty genes had altered DNA methylation in 22 of 25 cases. Aberrant methylation of CDKN2B and TIMP3 was most frequent. Promoter hypermethylation of BRCA2, APC, CDKN2A and CDKN2B was detected in 2 RRP cases with subsequent progression to SCC. Of the 25 cases, 22 were positive for HPV-6, 2 for HPV-11 and 1 for HPV-16 and 33.

CONCLUSIONS:

Consistent aberrant methylation of multiple tumor suppressor genes contributes to the pathogenesis of laryngeal papillomas. Persistent aberrant DNA methylation events in 2 RRP cases that progressed to cancer indicate an epigenetic monoclonal progression continuum to SCC.

PMID: **21603083** [PubMed]

Case Rep Oncol. 2011 Mar 23;4(1):162-71.

Recurrent respiratory papillomatosis: a rare chronic disease, difficult to treat, with potential to lung cancer transformation: apropos of two cases and a brief literature review.

Katsenos S, Becker HD.

Source

Department of Interdisciplinary Endoscopy, Thoraxklinik at Heidelberg University, Heidelberg, Germany.

Abstract

Recurrent respiratory papillomatosis (RRP), which is caused exclusively by human papilloma virus (HPV), is a rare condition characterized by recurrent growth of benign papillomata in the respiratory tract. The papillomata can occur anywhere in the aerodigestive tract but most frequently in the larynx, affecting both children and adults. The management of this entity remains still challenging since no specific definitive treatment exists. Nevertheless, novel surgical interventions as well as several adjuvant therapies have shown promising results in the long-term palliative management of this debilitating disease. Despite its mostly benign nature, RRP may cause significant morbidity and mortality because of its unpredictable clinical course and especially its tendency, albeit infrequent, for malignant transformation. In this article, we present two patients with RRP; one underwent bronchoscopic laser ablation in combination with inhaled interferon-alpha administration that led to a long-term regression of the disease while the other patient was diagnosed with transformation to squamous cell lung carcinoma with fatal outcome. We include a review of the current literature with special emphasis on RRP management and the potential role of HPV in the development of lung cancer.

PMID: **21526134** [PubMed]

Arch Otolaryngol Head Neck Surg. 2011 Apr;137(4):368-72.

Association of asthma with clinically aggressive recurrent respiratory papillomatosis.

Robb PK Jr, Weinberger PM, Perakis H, Li A, Klein AM, Johns MM 3rd, Adkins LK, Postma GN.

Source

Department of Otolaryngology and Center for Voice and Swallowing Disorders, Georgia Health Sciences University, 1120 15th St, Room BT4633, Augusta, GA 30912, USA.

Abstract

OBJECTIVE:

To determine whether there is an association between the presence of asthma and a clinically aggressive disease course in patients with recurrent respiratory papillomatosis (RRP).

DESIGN:

Retrospective multi-institutional cohort study (level III evidence).

SETTING:

Two academic medical centers in the southeastern United States.

PATIENTS:

Adult patients with RRP treated at the Georgia Health Sciences University or at the Emory University School of Medicine between January 1998 and December 2009. Excluded from the study were adult patients who had been diagnosed as having RRP when they were a child (<18 years).

MAIN OUTCOME MEASURES:

The primary outcome measure was the presence of a clinically aggressive RRP disease course (defined as distal spread of disease, >4 procedures performed in 12 months, or progression to laryngeal squamous cell carcinoma). The secondary outcome measure was the frequency of required surgical interventions.

RESULTS:

Identified were 90 patients with RRP (age range at first diagnosis, 19.1-86.4 years). Seventeen patients had aggressive disease, and 73 patients had nonaggressive disease. Seven patients had a history of asthma, 5 of whom were using daily inhaled corticosteroids. An association was noted between the presence of asthma and aggressive RRP, which was found in 57% (4 of 7) of patients with asthma vs 16% (13 of 83) of patients without asthma ($P = .02$). Patients with asthma using daily inhaled corticosteroids were especially likely to have aggressive RRP, which was

found in 80% (4 of 5) of corticosteroid users vs 15% (13 of 85) of nonusers (P = .004).

CONCLUSIONS:

Patients with asthma, particularly those using daily inhaled corticosteroids, may have a more clinically aggressive RRP course. The cause of this association is unclear, and clinical recommendations should not yet be made based on these data.

PMID: **21502475** [PubMed - indexed for MEDLINE]

Laryngoscope. 2011 Apr;121(4):846-51. doi: 10.1002/lary.21332. Epub 2011 Mar 11.

Clinical features, health-related quality of life, and adult voice in juvenile-onset recurrent respiratory papillomatosis.

Ilmarinen T, Nissilä H, Rihkanen H, Roine RP, Pietarinen-Runtti P, Pitkäranta A, Aaltonen LM.

Source

Department of Otorhinolaryngology-Head and Neck Surgery, Group Administration, Helsinki, Finland. taru.t.ilmarinen@hus.fi

Abstract

OBJECTIVES/HYPOTHESIS:

To determine clinical features, health-related quality of life, and adult voice in patients with a history of juvenile-onset recurrent respiratory papillomatosis (JORRP).

STUDY DESIGN:

Case-control study.

METHODS:

All 32 patients with JORRP treated at Helsinki University Hospital between 1975 and 1994 were invited to an outpatient visit in spring 2008, and 18 of them (56%) entered the study. Each patient had an age- and gender-matched control subject with similar smoking habits. Videolaryngostroboscopy was performed and voice quality determined by acoustic and perceptual analysis. Voice-quality characteristics of the whole patient group and the recurrence-free patients were examined separately.

Subjective voice-related disability was studied with voice handicap index (VHI) and health-related quality of life with a 15D questionnaire.

RESULTS:

Acoustic analysis showed that patients had statistically significantly higher values in percent jitter, percent shimmer, and noise-to-harmonics ratio. Perceptual analysis indicated higher scores for patients in overall grade, roughness, breathiness, and strain. Acoustic and perceptual values for recurrence-free patients (n = 14) were also significantly higher than those for their matched paired controls. No statistically significant differences emerged for handicap related to voice or to health-related quality of life. Four study patients (22%) had undergone tracheotomy, indicating severity of juvenile-onset disease.

CONCLUSIONS:

JORRP is a risk factor for permanent laryngeal pathology and voice-disturbances in adulthood.

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PMID: **21400536** [PubMed - indexed for MEDLINE]

Ann Otol Rhinol Laryngol. 2011 Jan;120(1):17-20.

Initial experience using propranolol as an adjunctive treatment in children with aggressive recurrent respiratory papillomatosis.

Maturo S, Tse SM, Kinane TB, Hartnick CJ.

Source

Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts 02114-3914, USA.

Abstract

We performed a retrospective chart review with a 6-month follow-up to examine the initial use of propranolol as an adjunctive treatment in children with severe recurrent respiratory papillomatosis. This is the first such report. Two of 3 children with severe recurrent respiratory papillomatosis demonstrated a response to oral propranolol therapy, as evidenced by an improved voice and by an increased time between

surgical interventions. One child demonstrated no response to propranolol, and medication was halted. Both children who demonstrated a response had undergone more than 10 surgical interventions in the previous year, along with prior treatment including surgical excision and adjuvant therapy. Both children more than doubled the interval between treatments after propranolol administration, and the parents of both children noted marked improvement of the child's voice as measured by their Pediatric Voice-Related Quality of Life score (from 40 to 67.5 in one child and from 27 to 60 in the other child). No child experienced hypoglycemia or blood pressure abnormalities. We conclude that initial use of propranolol as an adjunctive measure in severe recurrent respiratory papillomatosis shows it to have some efficacy in delaying surgical intervention and improving voice. Previous reports have demonstrated relatively safe use of propranolol in children with hemangiomas. Further studies are needed to determine the long-term effectiveness, dosing strategies, and side-effect profile of propranolol for treatment of recurrent respiratory papillomatosis.

PMID: **21370676** [PubMed - indexed for MEDLINE]

Ugeskr Laeger. 2011 Feb 14;173(7):506-7.

[Malignant degeneration in laryngeal papillomatosis].

[Article in Danish]

Grøn AL, Schultz JH, Abildgaard J.

Source

Øre-næse-hals-afdelingen, Vejle Sygehus, 7100 Vejle, Denmark.

Abstract

Recurrent respiratory papillomatosis (RRP) is considered a benign disease although malignant transformation is well-described. The involvement of human papilloma virus (HPV) in malignant transformation is still being discussed. We present a case of rapid malignant transformation of RRP in a 29-year-old male. The tumour as well as biopsies from his previous laryngeal papillomas tested positive for HPV 16. Introduction of a quadrivalent HPV vaccine with a view to preventing cervical cancer may also reduce RRP, and subsequently possibly also the incidence of head-and-neck cancers.

PMID: **21320416** [PubMed - indexed for MEDLINE]

J Laryngol Otol. 2011 Apr;125(4):402-4. Epub 2011 Jan 31.

Novel method of intralesional cidofovir injection into laryngotracheal papillomata.

Sahota RS, Uddin FJ, Al-Shukri J, Moir AA.

Source

Department of Otorhinolaryngology, Leicester Royal Infirmary, UK. rss8@le.ac.uk

Abstract

Laryngeal papillomatosis is characterised by multiple papillomata affecting the upper respiratory tract. This condition is difficult to treat due to its recurrent nature. Treatment often involves surgical debulking. A number of non-surgical treatments have been reported. Intralesional cidofovir, a cytosine nucleoside analogue with antiviral activity, has been used in an attempt to manage the condition. We present a novel technique of administering cidofovir in a case of recurrent laryngotracheal papillomata.

PMID: **21281536** [PubMed - indexed for MEDLINE]

Expert Opin Ther Pat. 2011 Mar;21(3):295-309. Epub 2011 Jan 21.

Advances in human papilloma virus vaccines: a patent review.

Cho HJ, Oh YK, Kim YB.

Source

Seoul National University, College of Pharmacy, Daehak-dong, Gwanank-gu, Seoul, South Korea.

Abstract

INTRODUCTION: Human papilloma virus (HPV) infection is the main factor associated with the development of cervical cancer. The currently available HPV vaccines, Gardasil and Cervarix, can prevent infection by certain HPV types, but not all. At present, research efforts are being devoted to developing more broad spectrum preventative vaccines, as well as therapeutic vaccines. AREAS

COVERED: Recent advances in HPV vaccine development are reviewed in this paper, with a focus on worldwide patents and patent applications. In principle, patents that have been granted since 2002 are covered. Exceptions are the patents pending at PCT stage and recent patent applications since 2009. Readers will gain insights into the cutting-edge technologies being used in the development and production of vaccines, as well as adjuvant systems. EXPERT OPINION: In the future, the use of mosaic virus-like particles (VLPs,) comprising at least one L1 protein of each HPV type, may be able to prevent infection by all HPV types while patented codon-optimization techniques and the use of edible or DNA-based vaccines may be good places to start for reducing costs. Future vaccines should ideally have both preventive and therapeutic efficacies. Enhanced immunogenicity could be achieved by the use of more effective adjuvants, such as nanoparticle-based delivery systems, or new classes of adjuvants.

PMID: **21250872** [PubMed - indexed for MEDLINE]

Arch Dis Child. 2011 May;96(5):476-7. Epub 2011 Jan 10.

Recurrent laryngeal papillomatosis: successful treatment with human papillomavirus vaccination.

Mudry P, Vavrina M, Mazanek P, Machalova M, Litzman J, Sterba J.

Source

Department of Paediatric Oncology, University Children's Hospital Brno, Cernopolni 9, Brno, Czech Republic. pmudry@seznam.cz

Abstract

The authors describe the case of a 5-year-old girl with recurrent laryngeal papillomatosis (RLP) due to human papillomavirus (HPV) type 11, who required frequent surgical treatment. Complete recovery occurred after HPV vaccination (Gardasil). Confirmed remission of RLP has continued during the 17 months of follow-up since vaccination. The authors conclude that HPV vaccination may represent a new therapeutic option in this situation.

PMID: **21220258** [PubMed - indexed for MEDLINE]

Paediatr Anaesth. 2010 Dec;20(12):1084-91. doi: 10.1111/j.1460-9592.2010.03447.x.

Airway management in pediatric patients undergoing suspension laryngoscopic surgery for severe laryngeal obstruction caused by papillomatosis.

Li SQ, Chen JL, Fu HB, Xu J, Chen LH.

Source

Department of Anesthesiology, The Eye Ear Nose and Throat Hospital, Fudan University, Shanghai, China.

Abstract

OBJECTIVES:

To review perioperative airway management and ventilation strategy during the surgical removal of papilloma under suspension laryngoscopy in pediatric patients with severe airway obstruction.

METHODS:

Seventy pediatric patients with degree III and IV laryngeal obstruction who underwent suspension laryngoscopy to remove laryngeal papillomatosis, between July 2005 and March 2009, were included in the study. All patients were intubated initially to secure the airway. Controlled ventilation through an endotracheal (ET) tube was used during the papilloma debulking near the glottis vera. Spontaneous ventilation or apneic technique was adopted based on the stage of the surgical procedure and the location of the remaining tumor. Hemodynamic parameters, pulse oxygen saturation (SpO₂), and CO₂ were closely monitored, and adverse events were recorded.

RESULTS:

The duration of the surgical operation and the duration of the extubation period were 5-35 min and 5-20 min, respectively. Thirty cases with degree III and twenty cases with degree IV laryngeal obstruction received inhalation induction. Sixteen cases with degree III laryngeal obstruction were given an intravenous induction. Four patients admitted with a comatose status were emergently intubated without any anesthetics. The ET tube size was determined by assessing the opening through the tumor mass or glottic aperture under direct laryngoscopy. SpO₂ was maintained above 97% after the airway was secured and sufficient ventilation established. Controlled ventilation was used in all children during the bulk removal of tumor. Spontaneous respiration and apneic technique were adopted for the removal of the

remaining tumor in the hypolarynx or trachea in 16 and 28 cases, respectively. Three patients had to be re-intubated postoperatively because of persistent desaturation or laryngospasm.

CONCLUSION:

Key points of perioperative airway management in pediatric patients with papillomatosis-induced severe laryngeal obstruction include careful preoperative airway evaluation; the proper choice of induction methods, and ET tube size; maintenance of an adequate depth of anesthesia; and flexible ventilation strategy, continuous and close monitoring during the extubation and postextubation period; and prompt management of adverse events.

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PMID: **21199117** [PubMed - indexed for MEDLINE]

Otolaryngol Head Neck Surg. 2010 Nov;143(5):685-90.

The quality of life and health utility burden of recurrent respiratory papillomatosis in children.

Chadha NK, Allegro J, Barton M, Hawkes M, Harlock H, Campisi P.

Source

Division of Pediatric Otolaryngology-Head and Neck Surgery, BC Children's Hospital, Vancouver, British Columbia, Canada. nchadha@cw.bc.ca

Abstract

OBJECTIVE:

In this study we 1) measured the impact of juvenile-onset recurrent respiratory papillomatosis on health-related quality of life, voice-related quality of life, and family psychosocial well-being; and 2) compared these different measures, exploring their intercorrelation and their correlation with clinical disease severity.

STUDY DESIGN:

Cross-sectional qualitative study.

SETTING:

Tertiary academic pediatric hospital.

SUBJECTS AND METHODS:

Twenty consecutive children with active juvenile-onset recurrent respiratory papillomatosis (JoRRP) were included. Standardized interviews were performed on parents and children with the use of four validated tools: the Health Utilities Index version 3; the Pediatric Voice-Related Quality of Life survey; the Impact on Family Scale; and a visual analogue health preference measure. Clinical disease severity and demographic data also were collected.

RESULTS:

Subjects (13 male, 7 female) had a median age of 9.2 years, median age of JoRRP onset of 3.8 years, and averaged four procedures per year of disease. Mean health utility was 0.76 (95% confidence interval 0.68-0.84) on a scale of 0 (death) to 1 (perfect health). Marked impact on voice-related quality of life and family psychosocial health also was identified. Health burden correlated poorly with existing methods of severity scoring.

CONCLUSION:

This is the first study to use validated measures of health utility, voice-related quality of life, and psychosocial impact. This information has public health implications, providing essential parameters for accurate modeling studies and cost-utility analysis of future interventions, including different human papilloma virus vaccination strategies.

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PMID: **20974340** [PubMed - indexed for MEDLINE]

Sex Health. 2010 Sep;7(3):253-61.

Estimating the prevalence of and treatment patterns for juvenile onset recurrent respiratory papillomatosis in Australia pre-vaccination: a pilot study.

Novakovic D, Cheng AT, Cope DH, Brotherton JM.

Source

St Luke's Roosevelt Hospital, New York, NY 10019, USA.

Abstract**BACKGROUND:**

Recurrent respiratory papillomatosis (RRP) causes serious morbidity. RRP in Australia may be eliminated in the near future following the implementation of a national vaccination program using a human papillomavirus (HPV) vaccine that protects against infection with HPV types 6 and 11, those responsible for RRP. Baseline data on RRP prevalence and disease burden in Australia are lacking.

METHODS:

Three study methods were used to estimate the burden of juvenile onset RRP in Australia. We conducted a retrospective chart review of RRP cases treated at The Children's Hospital at Westmead over 10 years, examined the coding of these cases, and then calculated and applied the positive predictive value of the codes to national data to estimate the prevalence of RRP in Australia. We also conducted an online survey of otolaryngologists in Australia who manage RRP.

RESULTS:

Nineteen patients were treated at the hospital over 10 years, involving 359 admissions. We estimate that between 33 and 56 RRP cases aged <20 are being treated nationally per year (0.6-1.1 per 100 000 persons), with children 5-9 years having a higher estimated rate of 1.2-1.8 per 100 000. Among 39 otolaryngologists treating juvenile onset RRP, the majority (73%) treated RRP in a paediatric tertiary hospital, and used the microdebrider for ablation of lesions.

CONCLUSIONS:

Our estimates of RRP disease burden agree with international estimates. As a small number of clinicians treat RRP nationally, we believe that establishment of a national RRP register is both feasible and necessary to monitor the impact of vaccination.

PMID: **20719212** [PubMed - indexed for MEDLINE]

Int J STD AIDS. 2010 Jun;21(6):381-5.

Recurrent respiratory papillomatosis: an uncommon but potentially devastating effect of human papillomavirus in children.

Donne AJ, Clarke R.

Source

University of Liverpool, UK. Adam.Donne@alderhey.nhs.uk

Abstract

Human papillomavirus (HPV) causes disease not only in the genital tract, but also in the larynx. Within the larynx HPV 6/11 causes recurrent respiratory papillomatosis (RRP). RRP is relatively uncommon, yet it is devastating for the patient who requires many surgical procedures over years to control it. The cost of HPV-related genital tract disease is thought to be around pound31 million per annum, whereas RRP costs in the region of pound4 million annually despite RRP being comparatively rare. The HPV vaccination programme has brought great hope, although it is unfortunate that the current UK programme only targets high-risk HPV. Targeting both low- and high-risk HPV would have had additional benefits for the UK.

PMID: **20606216** [PubMed - indexed for MEDLINE]

Otolaryngol Pol. 2010 Mar-Apr;64(2):98-102.

[The schedule of intralesional papillomatosis treatment with cidofovir].

[Article in Polish]

Szyfter W, Wierzbicka M, Jackowska J, Bartochowska A, Banaszewski J.

Source

Katedra i Klinika Otolaryngologii i Onkologii, Laryngologicznej UM w Poznaniu.

Abstract***INTRODUCTION:***

Recurrent respiratory papillomatosis (RRP) is a rare disease in children and adults. It is characterized by proliferation of benign squamous cell papillomas within the respiratory-digestive tract, predominantly the larynx. Standard treatment consists of surgical excision of papillomata to maintain airway patency and voice quality. For last several years cidofovir is the most contemporary adjuvant anti-viral treatment for recurrent respiratory papillomatosis and its topical use is widely described.

MATERIAL AND METHODS:

Intralesional cidofovir therapy was given to 20 patients treated for laryngeal papillomas in the Department of Otolaryngology in Poznan between I-XII.2009. The

character of the lesion differed: from one anatomical site and moderate growth to four or five localizations with heavy extension. The number of cidofovir injections per patient varied from one to six times and the volume of solution ranges from 1-12 ml. The cidofovir injections were combined with laser or mechanical excision of the lesions. In disperse papillomata the injections administered in particular anatomical sites in 4-6 weeks period. In massive lesions injections were repeated in the same anatomical site.

RESULTS:

Complete remission was observed in 3 out of 20 patients. 12 patients show remission in a place of cidofovir injection. In 4 patients during the 4 week observation new foci of papillomatosis occurred. In two patients hepatic toxic side effect were observed.

CONCLUSIONS:

Intralesional cidofovir injection has been shown to be an effective and safe therapy for laryngeal papilloma and should be considered in those patients who experienced disease relapse.

PMID: **20568538** [PubMed - indexed for MEDLINE]

Arch Otolaryngol Head Neck Surg. 2010 Jun;136(6):561-5.

Use of 532-nm pulsed potassium titanyl phosphate laser and adjuvant intralesional bevacizumab for aggressive respiratory papillomatosis in children: initial experience.

Maturo S, Hartnick CJ.

Source

EPI, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114-3914, USA.

Abstract**OBJECTIVE:**

To describe the initial pediatric experience with intralesional bevacizumab (Avastin) treatment for children with severe, recurrent respiratory papilloma (RRP).

DESIGN:

Retrospective medical chart review.

SETTING:

Tertiary care multidisciplinary aerodigestive center.

PATIENTS:

Three children, aged 3 to 6 years, with severe RRP requiring more than 4 operative interventions in 1 year whose parents (or legal guardians) consented to adjuvant treatment with intralesional bevacizumab.

INTERVENTION:

All 3 children were treated as follows: surgical debridement with a microdebrider, pulsed potassium titanyl phosphate laser treatments, and adjuvant intralesional injections with bevacizumab (1.25 mg total).

MAIN OUTCOME MEASURES:

Time interval between operative interventions, Derkey severity scale for RRP, and pediatric voice-related quality of life (PVRQOL) scores.

RESULTS:

All 3 children demonstrated increased time between operative interventions. Two children had a substantial decrease in their Derkey score and improved PVRQOL scores. One child, although time between operative interventions improved, did not have any change in Derkey score and required further adjuvant therapy.

CONCLUSIONS:

Injectable bevacizumab appears to show some efficacy in prolonging the time between treatments and therefore reducing the number of treatments per year in children with severe RRP. However, before any meaningful conclusions can be drawn, further studies must be conducted in the form of head-to-head trials looking specifically at the issues of time between treatment intervals, efficacy of one adjunct over another, vocal outcomes, and whether several adjunctive treatments confer advantage over 1 treatment. In-depth and careful informed consent is mandatory for these studies so that parents are aware of the risks and benefits (known and unknown) before such individualized decisions are made.

PMID: **20566906** [PubMed - indexed for MEDLINE]

APMIS. 2010 Jun;118(6-7):494-509.

Current concepts on human papillomavirus infections in children.

Syrjänen S.

Source

Department of Oral Pathology and Oral Radiology, Institute of Dentistry and MediCity Research Laboratory, University of Turku, Finland. stina.syrjanen@utu.fi
<stina.syrjanen@utu.fi>

Abstract

Current evidence is strong enough to conclude that human papillomavirus (HPV) can be transmitted both sexually and non-sexually. The debate on HPV infections in children still continues but it is more focused on HPV prevalence than on transmission modes. HPV DNA detection in amniotic fluid, foetal membranes, cord blood and placental trophoblastic cells all suggest HPV infection in utero, i.e. prenatal transmission. Based on recent meta-analysis, vertical transmission occurs in approximately 20% of cases. Most of the mucosal HPV infections in infants are incident, persistent infections in oral and genital mucosa being found in less than 10% and 2% respectively. The mother seems to be the main transmitter of HPV to her newborn, but subsequent HPV infections are acquired horizontally via saliva or other contacts. Bimodal peak prevalence is seen for skin warts, oral papillomas and recurrent respiratory papillomatosis (RRP) in younger and older age groups, suggesting similar epidemiology. Of the clinical HPV diseases, juvenile-onset-RRP and genital condylomata are problematic; the former because of its life-threatening potential and the latter because of possible sexual abuse. HPV6 and 11 are the most common genotypes in both the lesions. Early in life, infections by the high-risk HPV genotypes may also remain persistent for a considerable period, and should be of considerable importance for HPV vaccination strategies.

PMID: **20553530** [PubMed - indexed for MEDLINE]

APMIS. 2010 Jun;118(6-7):455-70.

Recurrent respiratory papillomatosis: a complex defect in immune responsiveness to human papillomavirus-6 and -11.

Bonagura VR, Hatam LJ, Rosenthal DW, de Voti JA, Lam F, Steinberg BM, Abramson AL.

Source

Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, NY, USA. bonagura@lij.edu

Abstract

Recurrent respiratory papillomatosis (RRP) is a rare disease of the larynx caused by infection with human papillomaviruses (HPV) -6 or -11, associated with significant morbidity and on occasion mortality. Here we summarize our current understanding of the permissive adaptive and innate responses made by patients with RRP that support chronic HPV infection and prevent immune clearance of these viruses. Furthermore, we provide new evidence of T(H)2-like polarization in papillomas and blood of patients with RRP, restricted CD4 and CD8 Vbeta repertoires, the effect of HPV-11 early protein E6 on T-cell alloreactivity, enriched Langerhans cell presence in papillomas, and evidence that natural killer cells are dysfunctional in RRP. We review the immunogenetic mechanisms that regulate the dysfunctional responses made by patients with RRP in response to HPV infection of the upper airway. In addition, we are identifying T-cell epitopes on HPV-11 early proteins, in the context of human leukocyte antigen (HLA) class II alleles enriched in RRP that should help generate a therapeutic vaccine. Taken together, RRP is a complex, multigene disease manifesting as a tissue and HPV-specific, immune deficiency that prevents effective clearance and/or control of HPV-6 and -11 infection.

PMID: **20553528** [PubMed - indexed for MEDLINE]

APMIS. 2010 Jun;118(6-7):450-4.

Epidemiology of recurrent respiratory papillomatosis.

Larson DA, Derkay CS.

Source

Department of Otolaryngology/Head and Neck Surgery, Eastern Virginia Medical School, Norfolk, VA 23507, USA.

Abstract

Recurrent respiratory papillomatosis (RRP) was first described in the 1800s, but it was not until the 1980s when it was convincingly attributed to human papilloma virus (HPV). RRP is categorized into juvenile onset and adult onset depending on presentation before or after the age of 12 years, respectively. The prevalence of this disease is likely variable depending on the age of presentation, country and socioeconomic status of the population being studied, but is generally accepted to be between 1 and 4 per 100 000. Despite the low prevalence, the economic burden of RRP is high given the multiple procedures required by patients. Multiple studies have shown that the most likely route of transmission of HPV in RRP is from mother to child during labor. Exceptions to this may include patients with congenital RRP who have been exposed in utero and adult patients who may have been exposed during sexual contact. Although cesarean section may prevent the exposure of children to the HPV virus during childbirth, its effectiveness in preventing RRP is debatable and the procedure itself carries an increased risk of complications. The quadrivalent HPV vaccine holds the most promise for the prevention of RRP by eliminating the maternal reservoir for HPV.

PMID: **20553527** [PubMed - indexed for MEDLINE]

Laryngoscope. 2010 Jun;120(6):1233-45.

The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database.

Campisi P, Hawkes M, Simpson K; Canadian Juvenile Onset Recurrent Respiratory Papillomatosis Working Group.

Collaborators (19)**Source**

Hospital for Sick Children, Toronto, Ontario, Canada.

Abstract**OBJECTIVES/HYPOTHESIS:**

To develop a national database of cases of juvenile onset recurrent respiratory papillomatosis (JoRRP) in Canada, to calculate trends in incidence and prevalence

of JoRRP from January 1994 to December 2007 at the national and regional level, and to mathematically model the natural history of JoRRP.

STUDY DESIGN:

Retrospective, multicenter study.

METHODS:

Patient demographics, clinical presentation, human papillomavirus status, method and timing of treatment, and indicators of disease severity were captured with a standardized case report form. Operative records were retrospectively scored using the Derkey-Coltrera staging system for each operative intervention. Trends in incidence and prevalence of JoRRP from 1994 to 2007 were calculated at a national and regional level using national population census data. A multivariable mixed effects linear model was used to explore the effect of surgery-specific variables on the intersurgical interval. Nonlinear least-squares regression was used to model the natural history of JoRRP.

RESULTS:

Development of a national database of children with JoRRP identified 243 cases who underwent 3,021 surgical procedures. The national incidence of JoRRP from 1994 to 2007 was 0.24 per 100,000 children aged 14 years and younger. The prevalence was 1.11 per 100,000 children. The natural history of JoRRP followed a nonlinear time course with 64% of cases having a decreasing annual rate of surgery over time.

CONCLUSIONS:

A Canadian national database of children with JoRRP was successfully developed. Modeling of the natural history of JoRRP may have important clinical and research implications.

PMID: **20513045** [PubMed - indexed for MEDLINE]

Otolaryngol Pol. 2010 Jan-Feb;64(1):31-6.

[Respiratory papillomatosis--new methods of treatment].

[Article in Polish]

Nowaczewska K, Wójtowicz P, Kukwa A, Ratajczak J, Tulibacki M.

Source

Klinika Otolaryngologii, Instytutu Stomatologii, Warszawskiego Uniwersytetu Medycznego.

Abstract**BACKGROUND:**

Respiratory papillomatosis is caused by HPV. The most common location in head and neck is larynx, palatine tonsils and arches of palate, uvula and mucosa oral and nasal cavity. The disease is benign but recurrent. The aim of this study was to estimate new methods of treatment respiratory papillomatosis based on intralesional injection of cidofovir into sites where papillomas had just been excised.

METHODS:

The purpose of the study were 59 patients treating in Otolaryngology Clinic Stomatology Department Medical University of Warsaw. The treatment was based on surgical excision of papilloma and after it intralesional injection of cidofovir in after 4-5 weeks.

RESULTS:

We observed the patients during 28 months. 41 patients had 4 times intralesional injection of cidofovir. 18 patients had increased number of injection of cidofovir because of recurrent papilloma. Rest of this group of the patients clinical studies showed remission disease.

CONCLUSION:

Surgery with intralesional cidofovir injection in the place after removal of papilloma is very effective methods. We observed that this treatment caused long lasting remission of papilloma recurrence.

PMID: **20476590** [PubMed - indexed for MEDLINE]

Clin Otolaryngol. 2010 Feb;35(1):60.

Should intralesional cidofovir be used for recurrent respiratory papillomatosis?

No abstract available.

Donne A, Rothera M, Homer J.

PMID: **20447168** [PubMed - indexed for MEDLINE]

Ann Otol Rhinol Laryngol. 2010 Apr;119(4):236-8.

Mucosal bridge and pitting of the true vocal fold: an unusual complication of cidofovir injection.

Man LX, Statham MM, Rosen CA.

Source

University of Pittsburgh Voice Center, Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

Abstract

We describe a unique complication of intralaryngeal cidofovir injection and present the case of a patient with recurrent respiratory papillomatosis in whom both a mucosal bridge and a pit of the true vocal fold developed after intralaryngeal cidofovir injection. A 40-year-old man presented with laryngeal papillomatosis 19 years after being treated with surgery and adjuvant radiotherapy for leiomyosarcoma of the cervical esophagus. The patient underwent 5 papillomatosis excisions combined with subepithelial injections of cidofovir to the bilateral true vocal folds at a concentration of 5 mg/mL without any complications. He subsequently received 2 higher-dose cidofovir treatments 6 weeks apart because of a poor response to the previous treatments. Two months later, there was evidence of a large mucosal bridge along the free edge of the right vocal fold and a deep pit in the lateral aspect of the same vocal fold. We conclude that repeated high-dose intralesional injection of cidofovir may result in significant morphological changes to the vocal fold, most likely due to mucosal injury.

PMID: **20433022** [PubMed - indexed for MEDLINE]

Eur J Pediatr. 2010 Aug;169(8):1017-21. Epub 2010 Mar 7.

Novel human papilloma virus (HPV) genotypes in children with recurrent respiratory papillomatosis.

Mammas IN, Sourvinos G, Vakonaki E, Giamarelou P, Michael C, Spandidos DA.

Source

Department of Virology, Faculty of Medicine, University of Crete, Heraklion, Crete, Greece.

Abstract**INTRODUCTION:**

Recurrent respiratory papillomatosis (RRP) is characterized by the presence of benign virally induced tumors of the larynx and respiratory epithelium that may obstruct the airway and tend to recur frequently. RRP is caused by the human papilloma virus (HPV), most frequently by HPV types 6 and 11. In this study, we present four cases of children with RRP in whom HPVs other than HPV-6 or HPV-11 were found.

MATERIAL AND METHODS:

In all four cases, HPV typing was performed by polymerase chain reaction (PCR) followed by restriction digestion (RFLP) in biopsy samples collected during surgery.

RESULTS:

In the first case, simultaneous HPV infection with types 13 and 39 was detected, while in the second case HPV-40 and HPV-56 were found. In cases 3 and 4, the biopsy samples were positive for unidentified 'low-risk' HPVs.

CONCLUSIONS:

The presence of novel HPV genotypes in children with RRP emphasizes the need for further investigation of the implication of these genotypes in the disease.

PMID: **20213305** [PubMed - indexed for MEDLINE]

Laryngoscope. 2010 Apr;120(4):698-702.

Degrees of dysplasia and the use of cidofovir in patients with recurrent respiratory papillomatosis.

Gupta HT, Robinson RA, Murray RC, Karnell LH, Smith RJ, Hoffman HT.

Source

Department of Otolaryngology, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242, USA.

Abstract**OBJECTIVES/HYPOTHESIS:**

Recurrent respiratory papillomatosis (RRP) is a benign disease characterized by recurrent lesions in the airway. The prevalence and degree of dysplasia that is

present in the natural course of RRP is not well established. Adjuvant therapies, such as cidofovir, have been tried with the goal of decreasing the interval between repeat surgical treatments, the mainstay of therapy. Although, the off-label use of cidofovir to treat RRP has been common, there have been concerns regarding carcinogenic transformation following the use of cidofovir. This study aims to explore the association between increasing degree of papilloma dysplasia and the use of cidofovir in the context of the natural progression of dysplasia in RRP.

STUDY DESIGN:

Retrospective case series.

METHODS:

Demographic data and surgical history were obtained through chart reviews for this retrospective case series of 13 patients with RRP who had histopathologic biopsies done before and after exposure to cidofovir. Pathologic data collected over 10 years from serial excisions at the University of Iowa Hospitals were reviewed by a single pathologist, and the highest degree of dysplasia was noted per excision time.

RESULTS:

Of the 176 specimens collected in these 13 patients with serial papilloma biopsies, 5.7% had no dysplasia, 57.4% had mild dysplasia (grade 1), 28.4% had moderate dysplasia (grade 2), and 8.5% had severe dysplasia (grade 3). A comparison of each patient's multiple biopsies across time suggested that the dysplastic grade was worse in two patients, better in four patients, and virtually unchanged in seven patients. There was no clear-cut pattern between the use of cidofovir and the degree of dysplasia over time.

CONCLUSIONS:

These results strongly suggest that intralesional cidofovir therapy does not correlate with worsening dysplastic progression. Dysplasia is relatively common in the setting of RRP; however, the prognostic significance of this finding is unknown. Additional research is needed to delineate the natural progression of dysplasia and its clinical significance in RRP, as well as the efficacy of cidofovir.

PMID: **20205173** [PubMed - indexed for MEDLINE]

Pak1 and Pak2 are activated in recurrent respiratory papillomas, contributing to one pathway of Rac1-mediated COX-2 expression.

Wu R, Abramson AL, Symons MH, Steinberg BM.

Source

Center for Oncology and Cell Biology, The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, NY, USA.

Abstract

Recurrent respiratory papillomas are premalignant tumors of the airway caused by human papillomaviruses (HPVs), primarily Types 6 and 11. We had reported that respiratory papillomas overexpress the epidermal growth factor receptor (EGFR), the small GTPase Rac1 and cyclooxygenase-2 (COX-2), and have enhanced nuclear factor-kappaB (NFkappaB) activation with decreased levels of IkappaB-beta but not IkappaB-alpha. We also showed that EGFR-activated Rac1 mediates expression of COX-2 through activation of p38 mitogen-activated protein kinase. We have now asked whether the p21-activated kinases Pak1 or Pak2 mediate activation of p38 by Rac1 in papilloma cells. Pak1 and Pak2 were constitutively activated in vivo in papilloma tissue compared with normal epithelium, and Rac1 siRNA reduced the level of both phospho-Pak1 and phospho-Pak2 in cultured papilloma cells. Reduction in Pak1 and Pak2 with siRNA decreased the COX-2 expression in papilloma cells, increased the levels of IkappaB-beta and reduced the nuclear localization of NF-kappaB, but had no effect on p38 phosphorylation. Our studies suggest that Rac1 --> Pak1/Pak2 --> NFkappaB is a separate pathway that contributes to the expression of COX-2 in HPV-induced papillomas, independently of the previously described Rac1 --> p38 --> COX-2 pathway.

PMID: **20131316** [PubMed - indexed for MEDLINE]

Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2009 Sep;23(18):832-6.

[Study on the correlation between EGFR-STAT3 signal pathway and laryngeal papilloma].

[Article in Chinese]

Wang X, Sun J.

Source

Department of Otolaryngology Head and Neck Surgery, the Affiliated Province Hospital, Anhui Medical University, Hefei, 230031, China.

Abstract**OBJECTIVE:**

To explore the relationship between the expression of EGFR and STAT3 in human laryngeal papilloma and its biological behavior.

METHOD:

Reverse transcription polymerase chain reaction(RT-PCR), immunohistochemical staining and Western blot were used to evaluate the mRNA and protein expression of EGFR and STAT3 (p-STAT3) in 42 laryngeal papilloma tissues and 15 samples of normal laryngeal tissue, and the relationship between the protein expression of them and clinic pathological parameters was also analyzed.

RESULT:

The mRNA expression levels of EGFR and STAT3 in laryngeal papilloma tissue were significantly higher than that in normal laryngeal tissue ($P < 0.05$, $P < 0.01$). Protein positive expression of EGFR and p-STAT3 were also detected in a significantly greater proportion of laryngeal papilloma than normal laryngeal tissue by immunohistochemistry and western blot ($P < 0.01$, $P < 0.05$). There was relationship between EGFR and p-STAT3 overexpression in laryngeal papilloma ($P < 0.05$). The expression p-STAT3 was correlated with the recurrence and canceration of laryngeal papilloma ($P < 0.05$).

CONCLUSION:

The EGFR-STAT3 signal transduction pathway may be involved in the pathogenesis of laryngeal papilloma,, and the persistent activation of STAT3 gene plays an important role in the recurrence and canceration of laryngeal papilloma.

PMID: **20120862** [PubMed - indexed for MEDLINE]

J Laryngol Otol. 2010 May;124(5):510-4. Epub 2009 Dec 11.

Radiofrequency coblation for treatment of advanced laryngotracheal recurrent respiratory papillomatosis.

Carney AS, Evans AS, [Mirza S](#), [Psaltis A](#).

Source

Department of Otolaryngology - Head and Neck Surgery, Flinders Medical Centre and Flinders University, Adelaide, South Australia, Australia.

Abstract**BACKGROUND:**

A variety of treatment modalities are currently used to treat recurrent respiratory papillomatosis. We aimed to study the efficacy of radiofrequency cold ablation (coblation) for the treatment of laryngotracheal recurrent respiratory papillomatosis, by comparing treatment intervals for coblation and CO2 laser vaporisation.

METHOD:

Retrospective case series of adult patients with advanced laryngotracheal recurrent respiratory papillomatosis.

RESULTS:

Six patients were treated for at least two years by CO2 laser vaporisation with or without intralesional cidofovir. All six subsequently underwent treatment with radiofrequency coblation with or without intralesional cidofovir. Coblation resulted in longer periods between interventions, compared with CO2 laser ($p = 0.03$).

CONCLUSION:

Radiofrequency coblation appears to be an attractive alternative technique to CO2 laser for the surgical treatment of advanced laryngotracheal papillomata.

PMID: **20003595** [PubMed - indexed for MEDLINE]

Antivir Ther. 2009;14(7):939-52.

Potential risk factors associated with the use of cidofovir to treat benign human papillomavirus-related disease.

Donne AJ, Hampson L, He XT, Day PJ, Salway F, Rothera MP, Homer JJ, Hampson IN.

Source

Department of Otolaryngology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK.
ajdonne@doctors.org.uk

Abstract**BACKGROUND:**

Cidofovir is currently being used off-licence to treat different viral infections, such as benign low-risk human papillomavirus (HPV)-related recurrent respiratory papillomatosis (RRP). There are concerns over the safety of this practice as rat studies demonstrated a high malignant transformation rate. As yet, there are no clinical reports of cidofovir-induced malignant changes in humans.

METHODS:

Telomerase immortalised human keratinocytes (hTert) stably expressing E6 proteins from either low-risk HPV6b or high-risk HPV16 and vector control cells were treated with either low-dose (5 microg/ml) or higher dose (30 microg/ml) cidofovir for 2 days and the effects evaluated by clonogenic survival assays. Based on these results, gene expression microarray analysis was performed on cidofovir-treated low-risk E6 and vector cells before, during and after drug treatment, and the results verified by real-time PCR.

RESULTS:

Both low-risk and high-risk E6-expressing cells show significantly improved long-term survival compared with vector control cells when exposed to 5 microg/ml cidofovir for 2 days, (hTert T6E6 P=0.0007, hTert T16E6 P=0.00023 and hTert vector control P=0.62). Microarray and real-time PCR analyses of low-dose cidofovir-treated low-risk E6-expressing cells revealed changes in gene expression that are known to be associated with malignant progression, which were not observed in drug-treated vector control cells.

CONCLUSIONS:

This is the first report that cidofovir can both increase cell survival and induce alterations in gene expression that are known to be associated with malignant transformation in cells transduced only with the E6 gene from low-risk HPV. It is our belief that these data provide cause for concern over the off-license use of this drug to treat RRP.

PMID: **19918098** [PubMed - indexed for MEDLINE]

B-ENT. 2009;5(3):137-41.

Treatment results in adult-onset recurrent respiratory papillomatosis.

Verguts MM, Genbrugge E, de Jong FI.

Source

Department of Otorhinolaryngology, Head and Neck Surgery, University Hospitals Leuven, Belgium.

Abstract

PROBLEMS/OBJECTIVES: To assess remission rate, treatment results, and factors for remission in patients with adult-onset recurrent respiratory papillomatosis (AORRP).

METHODOLOGY:

In this retrospective study, the clinical and pathological data of 51 patients with AORRP, treated in University Hospitals between 1972 and 2006 were reviewed. The male-female ratio was 7:3. At diagnosis, the median age was 43 years, and the median retrospective Coltrera-Derkay Staging and Severity score was 6 (range, 2-28). Twenty-one patients (41%) received only surgical treatment. Thirty patients (59%) were treated with surgery and adjuvant intralesional cidofovir.

RESULTS:

At the time of analysis in December 2006, 69% of the patients were in remission. Of those, 46% had been treated with adjuvant cidofovir. Of the patients who were not in remission, 87% had been treated with adjuvant cidofovir. This difference was statistically significant ($p = 0.005$). No significant difference was found between the remission group and the non-remission group for the factors age, gender, smoking habits, alcohol habits, GERD, severity and duration of therapy.

CONCLUSIONS:

AORRP was curable in most patients after long intensive treatment, with a general remission rate of 69%. Cidofovir was a negative factor for remission ($p = 0.005$). No other statistically significant factors for remission were found. Although a control group was present, it was not possible to perform a randomized study with comparable groups. A well-designed placebo-controlled, double-blinded, randomized trial to assess the outcomes of adjuvant intralesional cidofovir therapy for RRP would be valuable.

PMID: **19902848** [PubMed - indexed for MEDLINE]

Laryngoscope. 2010 Jan;120(1):188-92.

Patient reported voice outcome in recurrent respiratory papillomatosis.

van Nieuwenhuizen AJ, Rinkel RN, de Bree R, Leemans CR, Verdonck-de Leeuw IM.

Source

Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands.

Abstract

OBJECTIVES/HYPOTHESIS:

To assess the impact of patient reported voice outcome on quality of life and emotional functioning in patients treated for recurrent respiratory papillomatosis (RRP).

STUDY DESIGN:

Cross-sectional.

METHODS:

All adult patients treated for RRP between 1984 and 2008 were asked to participate. Outcome measures were obtained from questionnaires including VHI (Voice Handicap Index), HADS (Hospital Anxiety and Depression Scale), 36-Item Short Form Health Survey (SF-36), and Utrechtse Coping List.

RESULTS:

Out of 45 included patients, 34 (22 males, 12 females) participated (76%). Mean age was 52 years (range, 25-85 years). RRP was located only in the larynx in 90% of the cases. Adult onset RRP was diagnosed in 29 cases, juvenile onset RRP in 5. Median number of surgical procedures was five (range, 1-17). In this study cohort, 68% scored above the VHI cutoff point, and 18% had an increased risk for depression or anxiety disorders (HADS). VHI scores were related to age, time between consecutive surgeries, time since last surgery, and passive coping. They were not related to gender, onset of RRP, or location. VHI scores were related to the SF-36 subscales social functioning ($r = -0.43$) and mental health ($r = -0.43$).

CONCLUSIONS:

Patients with RRP often report voice problems in daily life, and this is related to (a passive) coping style, social functioning, and mental health. Psychosocial intervention targeting an adaptive coping style may be beneficial in selected cases.

PMID: **19877192** [PubMed - indexed for MEDLINE]

Ann Otol Rhinol Laryngol Suppl. 2009 Sep;201:1-13.

Microlaryngoscopic and office-based injection of bevacizumab (Avastin) to enhance 532-nm pulsed KTP laser treatment of glottal papillomatosis.

Zeitels SM, Lopez-Guerra G, Burns JA, Lutch M, Friedman AM, Hillman RE.

Source

Department of Surgery, Harvard Medical School, Center for Laryngeal Surgery and Voice Rehabilitation, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.

Abstract**OBJECTIVES:**

Photoangiolytic lasers effectively treat glottal papillomatosis, but do not reliably prevent recurrence. Therefore, sublesional injections of the antiangiogenic agent bevacizumab (Avastin) were given to assess the effect on disease recurrence and phonatory function.

METHODS:

A retrospective investigation was done in a pilot group of 10 adult patients with bilateral glottal papillomatosis who had prior angiolytic laser treatment with established patterns of recurrence. The patients underwent 5 bevacizumab injections (5 to 10 mg) into the diseased vocal folds along with 532-nm pulsed KTP laser photoangiolytic treatments 4 to 6 weeks apart. Their disease resolution was compared to findings from prior laser treatment alone, and objective measures of vocal function (acoustic, aerodynamic, Voice-Related Quality of Life survey) were obtained.

RESULTS:

All 10 patients had a greater than 90% reduction in recurrence. Four of the 10 had resolution. Four of the 10 have limited recurrent or persistent disease, receive

injections of bevacizumab at 8- to 12-week intervals, and have not required laser treatment. Two of the 10 have ongoing periodic office-based KTP laser treatment along with bevacizumab injections. No patient has required microlaryngeal surgery with general anesthesia, and all 10 have had substantial improvement in vocal function.

CONCLUSIONS:

This pilot investigation provides preliminary evidence that bevacizumab injections enhance photoangiolytic laser treatment of glottal papillomatosis while enhancing phonatory function. Coupling an antiangiogenesis agent with pulsed KTP laser photoangiolysis is conceptually promising, since the mechanisms of action are complementary.

PMID: **19845188** [PubMed - indexed for MEDLINE]

Int J Pediatr Otorhinolaryngol. 2010 Jan;74(1):7-14. Epub 2009 Oct 1.

The role of HPV type in Recurrent Respiratory Papillomatosis.

Donne AJ, Hampson L, Homer JJ, Hampson IN.

Source

Department of Otolaryngology, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, L12 2AP, United Kingdom. ajdonne@doctors.org.uk

Abstract

OBJECTIVE:

Human Papillomavirus (HPV) 6 and 11 are the aetiological agents responsible for Recurrent Respiratory Papillomatosis (RRP). There is general consensus that HPV11 results in more aggressive disease compared to HPV6.

METHOD:

Pubmed was searched using the terms respiratory papillomatosis, HPV 6 and HPV11. Comparisons were made in the outcomes of HPV6 versus HPV11 positive RRP disease.

RESULTS:

There are numerous sub-types or variants of both HPV6 and HPV11. These sub-types have different activities at least in-vitro. The numbers of different HPV types

within RRP tissue may be more extensive than initially appeared. This depends specifically upon the HPV types tested for.

CONCLUSION:

The clinical differences between HPV6 and HPV11 disease may not be accurately predictable as these viruses exist in numerous sub-types. Also, RRP tissue may contain more than one subtype or even be co-infected with other viruses that may influence outcome. In-vitro studies upon cell lines are a reasonable starting point for evaluation of these differences.

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PMID: **19800138** [PubMed - indexed for MEDLINE]

Otolaryngol Head Neck Surg. 2009 Oct;141(4):522-6.

Voice outcomes following repeated surgical resection of laryngeal papillomata in children.

Holler T, Allegro J, Chadha NK, Hawkes M, Harrison RV, Forte V, Campisi P.

Source

Department of Otolaryngology-Head and Neck Surgery, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

Abstract

OBJECTIVES:

1) To apply perceptual and acoustic voice assessments to children treated for juvenile-onset recurrent respiratory papillomatosis (JORRP); 2) to compare voice outcomes following treatment for JORRP using microdebrider versus carbon dioxide (CO₂) laser.

STUDY DESIGN:

Prospective cohort study.

SETTING:

This study was conducted at a tertiary pediatric academic center (March 2008-March 2009).

SUBJECTS AND METHODS:

Children with active JORRP were assessed using perceptual and acoustic voice analysis following treatment with either CO(2) laser or microdebrider. Outcome measures included overall severity rating, jitter, shimmer, and noise-to-harmonic ratio (NHR). The unpaired Student t test and Pearson correlation tests were used to explore the statistical significance of hypothesis tests.

RESULTS:

Eleven patients (8 male, 3 female) aged three to 17 years were enrolled. There were six children in the CO(2) laser cohort and five children in the microdebrider cohort. The immediate postoperative scores were significantly lower in the microdebrider cohort (vs the CO(2) cohort) for jitter, shimmer, NHR, and perceptual scores ($P < 0.05$), indicating a better voice quality in the microdebrider group. Jitter, shimmer, and NHR showed a significant positive correlation with the proportion of CO(2) laser procedures ($P < 0.05$).

CONCLUSION:

This is the first study to use perceptual and objective acoustic evaluations to compare voice outcomes following microdebrider or CO(2) laser treatment of JORRP. The results of this study suggest that treatment with the microdebrider results in a better immediate and early postoperative voice outcome. Moreover, the data demonstrate a correlation of worsening voice quality with increased exposure to the CO(2) laser.

PMID: **19786223** [PubMed - indexed for MEDLINE]

Chest. 2009 Sep;136(3):924-6.

Regression of recurrent respiratory papillomatosis with celecoxib and erlotinib combination therapy.

Limsukon A, Susanto I, Hoo GW, Dubinett SM, Batra RK.

Source

Division of Pulmonary and Critical Care Medicine, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA 90073, USA.

Abstract

Recurrent respiratory papillomatosis (RRP) can be difficult to manage. Symptoms are related to recurrent tracheobronchial papillomas and are usually treated with

bronchoscopic removal. Other modalities are added when the papilloma burden becomes too great or recurrence is too frequent, but with limited efficacy. We report a patient with progressive RRP that had become refractory to available therapy. Because papillomas overexpress epidermal growth factor receptor, along with increased expression of cyclooxygenase-2 and prostaglandin E2, it was reasoned that a combination therapy of erlotinib and celecoxib would be effective in controlling papilloma growth. After institutional approval and informed patient consent, this combination was initiated. There was a striking improvement in the number and appearance of respiratory tract papillomas, with elimination of the need for repeated papilloma removal. Pretreatment and posttreatment images document this response, and the improvement has now been maintained for nearly 2 years with effective therapy.

PMID: **19736197** [PubMed - indexed for MEDLINE]

Acta Otolaryngol. 2010 Feb;130(2):281-5.

Comparison of intravenous general anaesthesia vs endotracheal intubation in the surgical management of juvenile onset recurrent respiratory papillomatosis.

Lei W, Wen W, Su Z, Chai L, Feng X, Liu K, Jiang A, Zhu X.

Source

National Key Disciplines of Otorhinolaryngology, Otorhinolaryngology Hospital, Otorhinolaryngology Institute, First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, PR China.

Abstract

CONCLUSIONS:

Both intravenous general anaesthesia (IVGA) and general anaesthesia with endotracheal intubation (GA with ET) are applicable for the procedure of juvenile onset recurrent respiratory papillomatosis (JO-RRP). GA with ET was found to be better for JO-RRP patients with dyspnoea, as it provided better stabilization of the vital signs with fewer postoperative complications.

OBJECTIVES:

To evaluate the safety and efficacy of two different anaesthetic techniques in the removal of JO-RRP.

METHODS:

A total of 52 JO-RRP patients with mild dyspnoea were included in the study. Each case underwent two procedures, one by IVGA and the other by GA with ET. A total of 104 procedures were performed. The effectiveness and safety of the two anaesthetic techniques were pairwise compared.

RESULTS:

There were no significant differences in anaesthetic recovery time, operative time or postoperative voice quality between the two anaesthetic groups. However, significant differences in heart rate, oxygen saturation and carbon dioxide saturation were observed. Some patients who underwent IVGA developed apnoea (28.8%) and laryngeal spasm (19.2%). These complications were not observed in the GA with ET group.

PMID: **19685355** [PubMed - indexed for MEDLINE]

Pneumologie. 2009 Jul;63(7):387-9. Epub 2009 Jul 9.

[Treatment of respiratory papillomatosis--a case report on systemic treatment with bevacizumab].

[Article in German]

Nagel S, Busch C, Blankenburg T, Schütte W.

Source

Krankenhaus Martha-Maria, Halle-Dölau gGmbH, Klinik für Innere Medizin II, Halle.
S.Nagel@MarthaMaria-Halle.de

Abstract**BACKGROUND:**

Recurrent respiratory papillomatosis (RRP) is a known but rare disease, caused by human papilloma virus and characterised by multiple exophytic lesions and uncontrolled growth of papilloma in the respiratory tract. The most common complication of RRP is stenosis of the trachea. Medical therapeutic options have so far been less effective. However, inhibition of vascular endothelial growth factor (VEGF) by bevacizumab does appear to be an effective treatment option for RRP.

CASE REPORT:

The case of a 32-year-old male patient with RRP who has been treated for his symptomatic tracheal stenosis four times a year since 1996 is described. Only treatment by laser ablation showed any efficacy. Alternative treatment options did not show any effect. In May 2006 intrapulmonary lesions of RRP were also diagnosed but without any malignancy. From December 2007 to June 2008 the patient has been treated with bevacizumab. A visible regression of RRP and markedly less symptoms were observed. During this treatment no further laser ablation was necessary.

CONCLUSION:

Inhibition of VEGF by bevacizumab seems to offer a new and effective option in the medical management of RRP.

PMID: **19591084** [PubMed - indexed for MEDLINE]

Laryngoscope. 2009 Sep;119(9):1848-50.

An underreported complication of laryngeal microdebrider: vocal fold web and granuloma: a case report.

Mortensen M, Woo P.

Source

Department of Otolaryngology-Head and Neck Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA. mm6nj@virginia.edu

Abstract**OBJECTIVES/HYPOTHESIS:**

The microdebrider has become a valuable instrument for otolaryngologists. It is now used in the larynx for treatment of recurrent respiratory papillomatosis, laryngeal stenosis, and debridement of large cancers for airway control. There are few reported complications reported with the use of the microdebrider in the larynx.

STUDY DESIGN:

A case report.

METHODS:

A patient with a vocal fold polyp underwent removal of the polyp with a microdebrider at an outside institution. He presented to our clinic 2 months after the excision with a severely strained near aphonic voice. On rigid stroboscopic examination we saw a large anterior commissure laryngeal web with a granuloma. This was repaired by granuloma excision, web lysis, buccal graft, and laryngeal stent placement.

CONCLUSIONS:

The microdebrider is an extremely valuable tool for the otolaryngologist. Violation of the epithelium and the lamina propria with muscle exposure can result in serious damage to the vocal folds. When using powered instrumentation the surgeon should use the upmost caution in the larynx to avoid causing debilitating injury and scar with subsequent dysphonia.

PMID: **19554634** [PubMed - indexed for MEDLINE]

Laryngoscope. 2009 May;119(5):964-6.

Transoral trans-stomal microdebrider excision of tracheal papillomatosis.

Thorne MC, Zur KB.

Source

Department of Otolaryngology, Division of Pediatric Otolaryngology, University of Michigan, Ann Arbor, Michigan, USA. mthorne@med.umich.edu

Abstract**OBJECTIVES:**

To describe a technique for surgical removal of recurrent respiratory papilloma in the distal trachea in patients with an indwelling tracheostomy tube.

METHODS:

A transoral trans-stomal technique for removal of distal tracheal papilloma using a modified ventilating bronchoscope setup and a microdebrider with a rotatable Skimmer blade (XOMED Products, Jacksonville, Florida, USA).

RESULTS:

Surgical removal of papillomas in the distal trachea is a challenging procedure, involving potentially competing demands for visualization, instrumentation, and ventilation. Previously described methods for management of these challenging cases provide limited ability to deliver continuous oxygenation and ventilation during the procedure. The transoral trans-stomal technique overcomes these limitations in patients who have an existing tracheostomy.

CONCLUSIONS:

This technique allows for precise removal of papilloma in the distal trachea, while providing for excellent visualization and continuous oxygenation and ventilation of the patient.

PMID: **19358205** [PubMed - indexed for MEDLINE]

Dtsch Med Wochenschr. 2009 Apr;134 Suppl 2:S100-2. Epub 2009 Apr 7.

[Recurrent respiratory papillomatosis: indication for HPV vaccination?].

[Article in German]

Pawlita M, Gissmann L.

Source

Abteilung Genomveränderungen und Karzinogenese, Forschungsschwerpunkt Infektionen und Krebs, Deutsches Krebsforschungszentrum, Heidelberg. M.Pawlita@dkfz.de

Abstract

Recurrent respiratory papillomatosis (RRP) is a rare disease in children and adults. It is characterized by proliferation of benign squamous cell papillomas within the respiratory-digestive tract, predominantly the larynx. RRP is caused by oral infection with human papilloma virus (HPV) types 6 or 11. In aggressive disease, which within few months or even weeks requires multiple surgical interventions to remove papillomas, residual impairment of voice and breathing is almost inevitable.

Nowadays immune stimulation with interferon alpha or topic application of Cidofovir are recommended to lower the recurrence rate in aggressive disease but vaccination against mumps virus and photodynamic therapies has also been administered. The recently developed tetravalent HPV vaccine Gardasil induces neutralizing antibodies

against capsid antigens of the HPV types 16 and 18, which are associated with cervical cancer, as well as against types 6 and 11, which are associated with condylomata acuminata und respiratory papillomatosis. The vaccine has been shown to be safe and highly immunogenic. It can efficaciously prevent new genital infections by one of the four vaccine types as well as the epithelial lesions induced by them. However, the vaccine had no effect against pre-existing genital infections or lesions. Here we propose the hypothesis that HPV vaccination could have a therapeutic effect in RRP by preventing new papilloma formation at additional sites. First case reports on Gardasil vaccination in juvenile as well as adult onset RRP have become available and their serological findings are presented here. In view of the low risk of this adjuvant immunotherapy a larger controlled multicentric trial is proposed to verify this hypothesis.

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High-resolution ultrasound in the evaluation of pediatric recurrent respiratory papillomatosis.

Bryson PC, Leight WD, Zdanski CJ, Drake AF, Rose AS.

Source

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Abstract

OBJECTIVES:

To characterize the ultrasonographic appearance of laryngeal papillomatosis and to compare ultrasound with direct laryngoscopy and bronchoscopy, the criterion standard, for airway evaluation.

DESIGN:

Prospective, nonrandomized analysis of preoperative and postoperative airway ultrasound images.

SETTING:

Tertiary, university-based medical center.

PARTICIPANTS:

Eight patients (4 females and 4 males) with recurrent respiratory papillomatosis, with a mean age of 10.25 years and a mean of 14 surgical papilloma resections (range, 3-35).

INTERVENTION:

The patients underwent planned papilloma resections with ultrasound evaluation before formal endoscopic resection. Preresection ultrasound images of respiratory papillomas were evaluated.

MAIN OUTCOME MEASURES:

The ultrasonographic appearance of respiratory papillomas and pediatric airway anatomy.

RESULTS:

Respiratory papillomas appeared as discrete, hyperechoic lesions on the relatively hypoechoic background of the true vocal folds.

CONCLUSIONS:

Recurrent respiratory papillomas have a characteristic ultrasonographic appearance that seems to correlate with endoscopic findings. It seems that this modality holds promise for identifying pedunculated papillomas. Although direct laryngoscopy and bronchoscopy are the criterion standard, airway ultrasound may have a role in the early diagnosis of, surveillance of, and operative planning for recurrent respiratory papillomatosis. To our knowledge, this is the first study to describe the ultrasonographic appearance of papillomas and the first comparison of ultrasonographic and endoscopic airway images. This modality merits further study, and further investigation is ongoing.

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Expert Opin Pharmacother. 2009 Mar;10(4):645-55.

Pharmacotherapy of recurrent respiratory papillomatosis: an expert opinion.

Gallagher TQ, Derkay CS.

Source

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Abstract**BACKGROUND:**

Recurrent respiratory papillomatosis is caused by the human papillomavirus types (HPV) 6 and 11. It affects both children and adults. In a small number of cases, the disease can be very aggressive causing significant morbidity and possibly death. Surgical therapy is the primary treatment but in patients with aggressive disease, adjunctive therapy is initiated. The majority of these adjuncts center on immunomodulation, disruption of molecular signaling cascades or interruption of viral replication to help decrease the severity of the disease. Recently, a preventative vaccine has become available but data on its effectiveness will be at least a decade away. In the mean time, researchers are examining other vaccination strategies in the fight against HPV disease.

OBJECTIVE:

We will review the following pharmacotherapies used in the adjunct treatment of RRP: interferon, acyclovir, ribivirin, cidofovir, COX-2 inhibitors, retinoids, anti-reflux medications, zinc, indole-3-carbinol, therapeutic/preventative vaccines.

METHODS:

This is a review paper. Utilizing Medline and Pubmed from 1966 to present, the key words as well as the above listed adjunct treatments were searched for relevant papers.

CONCLUSION:

The evidence supporting each of these adjuncts varies with a majority having only case reports or cases-series to support their use. However, there is hope on the horizon with regard to the HPV vaccine and its potential to prevent future transmission of this disease.

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Intralesional injection of cidofovir for recurrent respiratory papillomatosis in children.

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Source

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Abstract**INTRODUCTION:**

Papillomatosis of the larynx appears as the result of an infection by the human papilloma virus (HPV). In children, the disease produces benign lesions, which grow rapidly and show a marked tendency to recur once removed. The course of the disease is unpredictable. Some patients can achieve spontaneous remission; however, in other cases the disease progresses violently and requires multiple operations. There is currently no effective therapy for recurrent respiratory papillomatosis (RRP). The basic goal of treatment is to preserve the patency of air passages while simultaneously preserving the phonatory and anatomical functioning of the larynx. Over the last 10 years, the possibility of a pharmacological treatment has been continually explored: in particular, the administration of locally passed cidofovir (first reported in a 1999 study by Pransky) to the larynx with papillomas is under current scrutiny. **GOAL OF STUDY:** The goal of the following study is to estimate the effectiveness of locally administered cidofovir for treatment of papillomas of the larynx in children.

PATIENTS AND METHODS:

From 2005 to 2007, 10 patients (seven boys and three girls) between the ages of 1-18 years were treated. Operations were executed using microlaryngoscopy (Karl-Storz endoscopy) with general anesthesia. Cidofovir was passed intralesionally with concentration 5-10mg/ml in quantity from 1 to 5mg/kg in a 4-week interval.

RESULTS:

Seven of the 10 patients achieved total remission 6 months after the completion of treatment, scoring 0 points on Derkay's scale. These patients underwent therapy with cidofovir from 6 to 13 months. Three months after the completion of treatment, three children suffered a recurrence of papillomas. Two of them are estimated at 3 points on Derkay's scale, while the third is estimated at 5 points.

CONCLUSIONS:

The results of the study indicate that intralesional injections of cidofovir can be an effective method of treatment for recurrent respiratory papillomatosis in children.

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Otolaryngol Clin North Am. 2009 Feb;42(1):57-70, viii.

Palliative aspects of recurrent respiratory papillomatosis.

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Source

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Abstract

Recurrent respiratory papillomatosis (RRP) is a chronic, frequently debilitating, and potentially life-threatening disease. Therapy for RRP has evolved from simply inserting a tracheotomy to provide an airway and plucking out papillomata with cup forceps to provide some degree of voice to the present-day far more sophisticated approaches, along with preventative measures that may someday offer the potential dramatically to decrease disease prevalence. Family dynamics and support and intentional structuring of office protocols to accommodate the unique nature of RRP are as essential as any operative intervention for saving and prolonging life. This article reviews recent developments in the management of RRP and highlights palliative approaches to case management for those patients who are not easily cured with initial endoscopic interventions.

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