RECURRENT RESPIRATORY PAPILLOMATOSIS

H Dutta
Ganesh Man Singh Memorial Academy of ENT and Head and Neck Studies, TU Teaching Hospital, Kathmandu, Nepal

Correspondence to:
Dr. Heempali Dutta
Ganesh Man Singh Bhawan
TU Teaching Hospital, Maharajgunj, Kathmandu, Nepal
E-mail: heempali@hotmail.com

Objective of this article was to review the current knowledge regarding the etiology, clinical presentation and therapeutic procedure available for recurrent respiratory papillomatosis(RRP). Representative articles were searched, selected and reviewed. Human papilloma virus type 6 and 11 accounts for majority of cases of RRP. Hoarseness, stridor, chronic cough, dyspnoea are common presenting clinical presentation of RRP. Surgery is the treatment of choice and use of CO_2 laser has been the mainstay of treatment modality. Recently photodynamic therapy, adjuvant therapy like antiviral therapy, immunotherapy and Human papilloma virus vaccines has shown efficacy in treatment of RRP.

Key words: recurrence, respiratory papillomatosis, human papilloma virus.

INTRODUCTION:

Recurrent Respiratory Papillomatosis (RRP) is a disease of viral etiology characterized by recurrent proliferations of benign squamous papillomas anywhere in respiratory tract from nasal vestibule to the terminal bronchi. Predominant site being vocal folds, tonsillar pillar, uvula where there is change of epithelium.[1] 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, mid-zone of the laryngeal surface of the epiglottis, upper and lower margins of the ventricle, undersurface of the vocal folds, carina and bronchial spurs.[2] Interestingly, virus can be detected in the normal mucosa adjacent to lesions. It is thought that this provides a reservoir for regeneration of new papillomata.The disease has bimodal age distribution. Juvenile onset peaks around three to four years of age and adult onset peaks around 20-30 years of age. The natural history of recurrent respiratory papillomatosis is highly variable. Clinical presentation is usually with hoarseness or with symptoms of airway obstruction. After presentation, the disease may undergo spontaneous remission or persist in a stable state, requiring only periodic endoscopies. It also may take a progressive form, with distal spread down the tracheobronchial tree. Remissions and exacerbations of RRP are extremely common in both juvenile and adult onset disease and are unpredictable. Recurrent disease has been reported to develop after as long as 31 years of complete remission. Despite much speculation in the past that remissions and even permanent regression of respiratory papillomatosis often correlate with puberty, this does not in fact appear to be the case. On the other hand, pregnancy is associated with accelerated papilloma growth and reactivation of latent disease.

AETIOLOGY:

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] RRP was confirmed to contain human papillomavirus (HPV) DNA in 1980 by Quick et al.[9,10] The human papillomavirus is a naked, double-stranded, icosahedrally-shaped virus with circular supercoiled DNA that belongs to the Papovavirus family. There are 90 subtypes of HPV known[2], but only a few commonly cause RRP. The subtypes which usually cause RRP 6 and 11, although other types have been found. HPV types 6 and 11 account for the majority of cases of RRP, with HPV 11 occurring most commonly (52–62%) and running the most aggressive clinical course, followed by HPV 6 (24–48%).[11-13] HPV types 16, 18, 31 and 33 have been rarely reported in RRP.[14] Malignant transformation in RRP has generally been reported in adults with other risk factors such as tobacco use or exposure to radiation, but is also found in children, occurring in 16% of those with lung involvement.[15,16] Transmission of RRP has classically followed different routes for Juvenile onset RRP and Adult onset RRP. In juvenile cases vertical transmission is thought to occur, with first-born children of lower socioeconomic status and teenage women with active genital HPV infections at greatest risk. Adult onset RRP, transmission occurs in patients with multiple oral sex partners. Caesarean delivery does not prevent every case of infection and is not routinely recommended with active HPV infection.[17,18]

CLINICAL PRESENTATION AND DIAGNOSIS:

Juvenile onset RRP commonly presents between two to four years of age with hoarseness, which may progress to stridor, increased work of breathing and eventually, complete airway obstruction. Less common presenting symptoms include chronic cough, recurrent pneumonia, dysphagia, failure to thrive, dyspnoea or acute life-threatening events. . Adult onset RRP peaks between 20 and 40 years of age, with a slight male predominance and generally have more benign clinical course than JORRP.[14,15] Patients should be assessed with a complete head and neck examination, including observation of general appearance and auscultation of the upper airway. Patients with signs of air hunger; including neck extension, leaning forward with forearm support of the upper body (the tripod position), nasal flaring, drooling, use of accessory muscles of respiration or cyanosis, may require expeditious operative intervention. Out patient evaluation will also include a flexible fibre optic examination of the upper airway. After application of a topical decongestant (with a topical anaesthetic in larger children or adults), the nasopharynx, oropharynx, hypopharynx, larynx and subglottis are sequentially evaluated. Care should be taken to closely examine the squamocolumnar junctions

of the airway, i.e. the limen nasi, the soft palate, the ventricle and the undersurface of the true vocal folds, as these transition zones have been shown to have a predilection for RRP manifestation.[14] Macroscopically, the papilloma can be pedenculated or sessile. Microscopically, the papilloma appears as exophytic lesion consist of multiple finger-like projections with a central fibrovascular core, which are typically covered by stratified squamous epithelium.

TREATMENT:

The main aim of treatment for RRP is the removal of papillomas and restoration of a normal airway at the same time minimizing trauma to the mucosa and vocal cords. The patients may require multiple surgical excision for restoration of airway and occasionally require tracheostomy. But tracheostomy is deferred as the there is a risk of distal spread of papilloma. The primary cause of papilloma extension to the lower airways appears to be iatrogenic, i.e. the tracheotomies performed in children with laryngeal papillomatosis (92.5% of cases). This was reported in a case group of 448 children with RRP treated in St. Vladimir Moscow Children's Hospital between 1988 and 2003.[31]

SURGICAL TREATMENT:

Powered microdebrider has become gold standard modality of treatment of RRP. This modality of treatment is better than other modalities as it allows gentle but comprehensive removal of papillomas with minimal contamination of the lower respiratory tract with blood or papilloma. There is no thermal injury and can be used in direct endoscopic control. Various clinical trials has shown that compared with CO2 laser, it has good disease clearance, shorter procedure & less postoperative pain. However long term results of these studies are still awaited.[3,4,5] Cold Steel Surgery microsurgical excision was the earliest transoral management option for RRP and is still a preferred treatment in Adult onset RRP with limited involvement. Standard microlaryngeal instruments and techniques may be utilized to completely excise laryngeal papillomata with good voice results, and in one recent series complete remission was observed in two year follow-up of six primary AORRP patients, although this treatment is not as effective in recurrent or extensive disease.[19,20]

LASER EXCISION:

CO2 laser has been the main stay of treatment and treatment of choice for treatment of RRP. At the present time, the control of respiratory papillomatosis is best achieved with periodic microsuspension laryngoscopy and carbon dioxide laser vaporization. This method has proved superior to other endoscopic techniques such as cup-forceps removal, cryosurgery, and suction diathermy. The laser permits a more precise and complete removal of disease, while providing effective hemostasis. These factors help to minimize the chance of acute postoperative airway obstruction, which had discouraged regular eradication of papillomas prior to the introduction of the CO2 laser. Despite the improvement over other endoscopic modalities, laser vaporization is certainly not without its risks. Aside from the attendant risks of hypoxia and airway obstruction during any endoscopic procedure on these patients, complications such as airway fire, pneumothorax, laryngeal and tracheal stenosis, and tracheocutaneous fistula have all occurred with this therapy. Late soft tissue complications like vocal fold fibrosis and stenosis, glottis webbing and arytenoids fixation has been reported in 35-45% cases.[6,7,8] It is also important to mention that HPV 6 and 11 viral DNA have been detected in the laser plume, which theoretically may pose a risk to health care workers. Specialized masks are available to help filter out viral particles. Newer ultrapulsed laser models with a micromanipulator allow for beam-shaping capabilities to form a dot, line, circle or arc to further increase the precision of tissue ablation. Fibre delivery systems are also being developed for the CO2 laser (Omniguide®, Inc., Cambridge, Massachusetts), which has shown good cutting efficacy and healing characteristics in early studies [21] and may provide additional flexibility for ablating papilloma disease in difficult locations endoscopically. Angiolytic lasers including the 585nm pulsed-dye laser (PDL) and the 532nm pulsed potassium–titanyl–phosphate (KTP) laser are popular emerging treatments for RRP. They are absorbed selectively by haemoglobin, causing selective tissue ablation in the highly vascular papilloma lesions, and allow serial office treatments in AORRP or co-operative older children. Early studies have shown favorable results both in efficacy of disease ablation and in preservation of underlying normal tissues and voice outcomes.[20,22,23]

PHOTODYNAMIC THERAPY:

Photodynamic therapy is based on the principle that rapidly proliferating tissue selectively takes up a photosensitizing agents when administered intravenously. These agents release tumoricidal oxygen derivative by laser light of appropriate wavelength. The various randomized control trial using dihematoporphyrinether and meso-tetra chlorine along with shows significant decrease in papilloma size.

ADJUVANT THERAPY:

Can be divided into antiviral therapy, immunotherapy, vaccines and gene therapy

ANTIVIRAL THERAPY:

Cidofovir is an acyclic nucleoside phosphonate. It causes inhibition of viral DNA polymerase essential for viral multiplication. Multiple case series have studied the efficacy of intralesional cidofovir, with 60% demonstrating favourable results and low numbers of nonresponders.[16,24,25] In addition to a relative lack of studies with a high level of evidence, concerns have also been raised regarding the carcinogenic potential of cidofovir as mammary adenocarcinomas were shown to occur in rats exposed to cidofovir. For this reason the task force on RRP has recommended limiting usage of adjuvant cidofovir to dosages less than 5mg/kg and only to severe recalcitrant cases. Multiple other adjuvant therapies have been tried with some benefit, but limitations in data preclude significant clinical conclusions. These include indole 3-carbinol, retinoids, alpha-interferon and photodynamic therapy.[24]

IMMUNOTHERAPY:

The quadrivalent HPV-recombinant vaccine is now in use for prevention of HPV infection, but is also under development to examine the therapeutic possibilities of this vaccine in RRP. Heat-shock protein E7 (HspE7) is the fusion protein of recombinant Hsp65 from Mycobacterium bovis and the E7 protein from HPV 16, although not currently commercially available, may have some clinical utility in the future.

HUMAN PAPILLOMA VIRUS VACCINES:

Work on an HPV vaccine began at multiple institutions in 1991. Currently, two vaccines have been developed and studied, but the quadrivalent HPV recombinant vaccine, which has shown efficacy against HPV 16 and 18 and HPV 6 and 11, has received US Food and Drug Administration (FDA) approval and recommendations by the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAOP) Infectious Disease Committee for implementation among school aged females.

REFERENCES:

1. Ullmann EV. On the aetiology of the laryngeal papilloma. ACTA Otolaryngologica. V:317, 1923.
2. Murray LN, Miller RH. Recurrent respiratory papillomatosis. Journal of the Louisiana State Medical Society. 150(10): 456-9, 1998 Oct.Ê
3. Patel N, Rowe M, Tunkel D. Treatment of recurrent respiratory papillomatosis in children with the microdebrider. Annals of Otology, Rhinology and Laryngology.2003;112:7-10.
4. Patel RS, Mackenzie. Powered laryngeal papillomatosis: a prelilimínary report. Clinical Otolaryngology andAllied Sciences. 2002;25:358-60.
5. Pasquale K, Wiatrak B, Woolley A, Lewis L. Microdebrider verses CO2 laser removal of respiratory papillomatosis: a prospective analysis. Laryngoscope. 2003;113:139-43.

6. Saleh EM. Complications of treatment of recurrent laryngeal papillomatosis with carbondioxide laser in children. Journal of Laryngology and Otology.1992;106:715-8.
7. Ossoff RH,Werkhaven JA, Dere H. Soft- tissue complication of laser surgery for recurrent respiratory papillomatosis. Laryngoscope . 1991;101:116-6.
8. Crockett DM, MvCabe BF, Shive CJ. Complications of laser surgery for recurrent respiratory papillomatosis. Annals of Otology, Rhinology and Laryngology.1987;96:639-44.
9. Quick CA, Watts SL, Krzyzek RA, et al., Relationship betweencondylomata and laryngeal papillomata. Clinical and molecular virological evidence, Ann Otol Rhinol Laryngol, 1980;89(5 Pt. 1):467–71.
10. Bauman NM, Smith RJ, Recurrent respiratory papillomatosis,Pediatr Clin North Am, 1996;43(6):1385–1401.
11. Draganov P, Todorov S, Todorov I, et al., Identification of HPV DNA in patients with juvenile-onset recurrent respiratory papillomatosis using SYBR Green real-time PCR, Int J Pediatr Otorhinolaryngol, 2006;70(3):469–73.
12. Wiatrak BJ, Wiatrak DW, Broker TR, et al., Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population, Laryngoscope, 2004;114(11 Pt. 2 Suppl. 104):1–23.
13. Rabah R, Lancaster WD, Thomas R, et al., Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus- 6-associated disease, Pediatr Dev Pathol, 2001;4(1):68–72.
14. Derkay CS, Darrow DH, Recurrent respiratory papillomatosis,Ann Otol Rhinol Laryngol, 006;115(1):1–11.
15. Stamataki S, Nikolopoulos TP, Korres S, et al., Juvenile recurrent respiratory papillomatosis: still a mystery disease with difficult management, Head Neck, 2007;29(2):155–62.
16. Rady PL, Schnadig VJ, Weiss RL, et al., Malignant transformation of recurrent respiratory papillomatosis associated with integrated human papillomavirus type 11 DNA and mutation of p53, Laryngoscope, 1998;108(5):735–40.
17. Bishai D, Kashima H, Shah K, The cost of juvenile-onset recurrent respiratory papillomatosis, Arch Otolaryngol Head Neck Surg, 2000;126(8):935–9.
18. Kosko JR, Derkay CS, Role of cesarean section in prevention of recurrent respiratory papillomatosis – is there one?, Int J Pediatr Otorhinolaryngol, 1996;35(1):31–8.
19. Zeitels SM, Sataloff RT, Phonomicrosurgical resection of glottal papillomatosis, J Voice, 1999;13(1):123–7.
20. Burns JA, Zeitels SM, Akst LM, et al., 532 nm pulsed potassium-titanyl-phosphate laser treatment of laryngeal papillomatosis under general anesthesia, Laryngoscope, 2007; 117(8):1500–1504.
21. Devaiah AK, Shapshay SM, Desai U, et al., Surgical utility of a new carbon dioxide laser fiber: functional and histological study, Laryngoscope, 2005;115(8):1463–8.
22. Mouadeb DA, Belafsky PC, In-office laryngeal surgery with the 585nm pulsed dye laser (PDL), Otolaryngol Head Neck Surg,2007;137(3):477–81.
23. Zeitels SM, Burns JA, Office-based laryngeal laser surgery with the 532-nm pulsed-potassium-titanyl-phosphate laser, Curr Opin Otolaryngol Head Neck Surg, 2007;15(6):394–400.
24. Chadha NK, James AL, Antiviral agents for the treatment of recurrent respiratory papillomatosis: a systematic review of the English-language literature, Otolaryngol Head Neck Surg, 2007; 136(6):863–9.
25. Soma MA, Albert DM, Cidofovir: to use or not to use?, Curr Opin Otolaryngol Head Neck Surg, 2008;16(1):86–90.
26. Derkay C; Multi-Disciplinary Task Force on Recurrent Respiratory Papillomas, Cidofovir for recurrent respiratory papillomatosis (RRP): a re-assessment of risks, Int J Pediatr Otorhinolaryngol, 2005;69(11):1465–7.
27. Derkay CS, Faust RA, Recurrent Respiratory Papillomatosis. In:Cummings CW, Flint PW, Haughey BH (eds), Otolaryngology Head and Neck Surgery, 4th edition, Philadelphia: Mosby, Inc.,2005.
28. Derkay CS, Smith RJ, McClay J, et al., HspE7 treatment of pediatric recurrent respiratory papillomatosis: final results of an open-label trial, Ann Otol Rhinol Laryngol, 2005;114(9):730–37.
29. Soldatski IL, Onufrieva EK, Steklov AM, Schepin NV (2005) Tracheal, bronchial, and pulmonary papillomatosis in children. Laryngoscope 115:1848–1854.
30. Shikowitz MJ, Abramson AL, Freeman K, Steinberg BM, Nouri M. Efficacy of DHE photodynamic therapy for respiratory papillomatosis :immediate and long term results. Laryngoscope. 1998;108:962-7.
31. Shikowitz MJ, Abramson AL, Steinberg BM, Devoti J, Bonaqura VR, Mullooly V et al. Clinical trial of photodynamic therapy with meso-tetra(hydroxyphenyl) chlorine for respiratory papillomatosis. Archives of otolaryngology- Head and Neck Surgery.2005;131:99-105.