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REVIEW

Juvenile-Onset Recurrent Respiratory Papillomatosis Diagnosis and Management – A Developing Country Review

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Abstract: Recurrent respiratory papillomatosis (RRP) is a condition caused by human papillomavirus (HPV), usually HPV types 6 and 11, which is characterized by recurrent papillomas of the respiratory tract, mainly the larynx. Patients usually present between the ages of 2 and 6 years. The initial presenting symptom is progressive dysphonia, followed by stridor and respiratory distress. Treatment consists of repeated microlaryngoscopic procedures to remove the papillomas as there is no cure. The poor availability and accessibility of appropriate healthcare services in developing countries are barriers to the early diagnosis and appropriate management of patients with juvenile-onset recurrent respiratory papillomatosis (JoRRP), requiring many patients to have a tracheostomy. The introduction of prophylactic vaccines that include HPV6 and HPV11 is necessary in order to reduce the incidence of JoRRP.

Keywords: recurrent respiratory papillomatosis, human papillomavirus, children, developing countries

Introduction

Recurrent respiratory papillomatosis (RRP) is a condition caused by human papillomavirus (HPV) that is characterized by recurrent papillomas of the respiratory tract, mainly the larynx.[1] Two clinical presentations of the disease are recognized – juvenile-onset RRP (JoRRP), where the condition occurs under 12 years of age, and adult-onset RRP (AoRRP). JoRRP predominates in sub-Saharan Africa,[2–4] in contrast to Europe and South America, where AoRRP predominates.[5,6]

Epidemiology

The incidence and prevalence of JoRRP in developing countries has been found to be similar to or slightly higher than that in developed countries (Table 1).[2,7–16] However these data are probably an underestimate as a result of patients not having symptoms severe enough to present, or dying as a result of upper airway obstruction prior to presentation.

Etiology

There are over 180 HPV types.[1] HPV types 6 and 11 are responsible for most cases of JoRRP, although other types, including high risk types have also been identified.[3–5,9,17–34] Transmission of HPV is believed to occur during birth from the mother as the fetus passes through an infected genital tract. Although a minority

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Table 1 Incidence and Prevalence of JORRP

Region	Incidence per 100,000 Children	Prevalence per 100,000 Children per Year
Free State, South Africa[1]	1.34	3.88
Lesotho[6]	0.49	1.04
Thailand[9]	2.8	
Denmark[10]	0.35	
Copenhagen, Denmark[11]	0.6	0.8
Funen and Jutland, Denmark[12]	0.38	
Norway[13]	0.17	
USA[14]	4.3	
Atlanta and Seattle, USA[15]	0.12–2.13	1.00–3.97
USA[16]	0.51 (Private) 1.03 (Public)	1.45 (Private) 2.93 (Public)
Canada[7]	0.24	1.11
Japan[9]	0.1	
Australia[8]		0.6–1.1

of mothers of children with RRP have a history of previous genital condylomata, most have histologic evidence of HPV infection.[35] Children whose mothers have a history of genital warts are at greatly elevated relative risk of developing RRP.[36] The triad of a firstborn child born by vaginal delivery to a teenage mother was first described by Kashima and has subsequently been found in a number of other studies.[4,21,29,37] Primigravid mothers are more likely to have a long second stage of labor with prolonged exposure to HPV in the birth canal, leading to a higher risk of infection in the first-born child.

Clinical Presentation

Patients generally present between the age of 2 and 6 years, with an approximately equal sex distribution.[2,4,7,16,30–33,38-40] Patients with HPV11 disease present at a significantly younger age than those with HPV6 disease.[2,20,21,27] The initial presenting symptom is progressive dysphonia, followed by stridor and respiratory distress.[4,29,30,38–41] Patients may be aphonic with respiratory distress on presentation. Other symptoms may include chronic cough, recurrent upper respiratory tract infections and hemoptysis.[30,32] Patients are often misdiagnosed as having asthma, laryngotracheobronchitis, foreign body aspiration or laryngomalacia.[3] In developing countries, as a result of the poor availability of healthcare services in general and ENT services in particular,[42–44] patients frequently present with upper airway obstruction and a history of hoarseness for many years.[3,4,30,40,41,45–51] In a South African study, all patients diagnosed in the private sector had only hoarseness on initial presentation, while 70.1% of patients diagnosed in the public sector also presented with stridor, with 51.9% being in respiratory distress.[40] Pulmonary hypertension and cor pulmonale may rarely occur as a result of chronic upper airway obstruction.[46,52]

The larynx is the most common site of involvement, with the trachea being the most common site of extralaryngeal involvement. Other extralaryngeal sites that may be involved include the oropharynx, nasopharynx, nose, oral cavity, and lung.[3] Between 5 and 48% of children with JoRRP develop distal spread.[53,54] Pulmonary involvement occurs in 3.3% of patients with JoRRP. The incidence of lung cancer in patients with pulmonary involvement is 16%, with most patients who develop lung cancer having HPV11 disease.[55]

Diagnosis

All patients with chronic hoarseness, stridor, and/or respiratory distress should undergo flexible fibreoptic laryngoscopy or direct laryngoscopy and biopsy.[56] Unfortunately the expertise and facilities to perform these procedures are not easily accessible in developing countries. The papillomas appears as exophytic, pedunculated masses that can be single or multiple (Figure 1). In developing countries with a high incidence of tuberculosis, laryngeal tuberculosis may mimic respiratory papillomatosis. Histologically, the papillomas are exophytic finger-like projections of stratified squamous epithelium supported by a connective tissue stroma with abnormal keratinization and basal cell hyperplasia.[32,34] Chest imaging by either chest x-ray or CT scan should be performed in patients with RRP, especially those with a clinical presentation suggestive of pulmonary involvement.[56]

Staging

The Derkay staging system is the most commonly used system to stage the disease.[57] This system comprises both a functional assessment of clinical features and anatomic assessment of disease distribution. A limitation of this staging system is that, although it is effective for describing the presence of disease, the number of sites involved and the bulkiness of each lesion, it does not distinguish the different degrees of severity within a site.[58] A higher anatomical score is associated with a shorter intersurgical interval.[16]

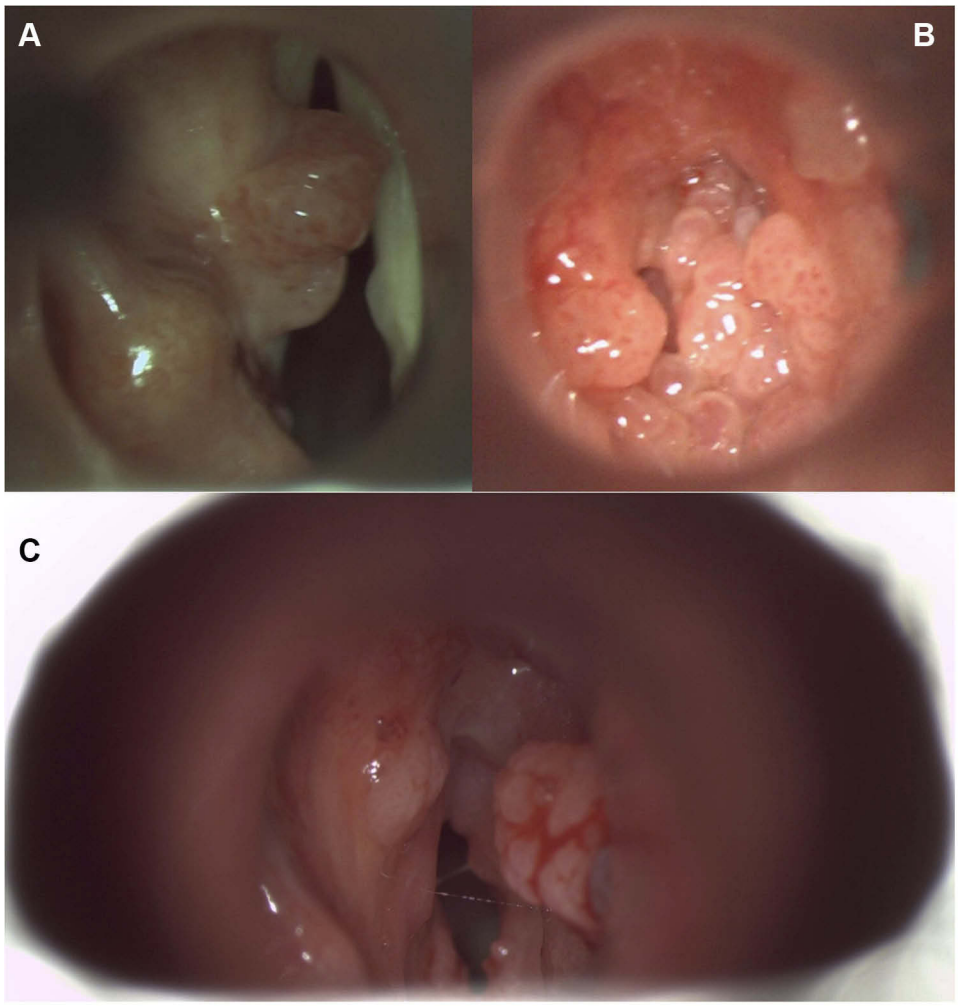

Figure 1 (**A-C**). Direct laryngoscopy view of laryngeal papillomas.

Disease Course

The clinical behavior of laryngeal papillomatosis is unpredictable. In most patients, the frequency of surgery decreases over time, but in approximately one-third of cases the surgical frequency remains constant or increases.[7,16,39,59] Although most patients eventually go into remission, in some the disease persists.[32] Patients may have recurrence after many years of remission as the latent viral infection persists in the laryngeal tissue.[34] No markers have been identified to predict which patients will go into remission or when this will occur. At least 50% of children with RRP require more than 10 procedures to control their disease, and 7% of patients require more than 100 operations during their lifetime.[13] The recurrent and persisting nature of the disease and dysphonia that occurs adversely affects patients' quality of life.[60,61]

Disease Aggressiveness

Most studies have found HPV11 disease to be more aggressive than HPV6 disease.[20,23–27,29,31,33] HPV typing has therefore been suggested as a possible means of predicting disease aggressiveness.[29,31,62] However, younger age at diagnosis has been found to be associated with more aggressive disease, and has also been found to be a more significant marker of disease aggressiveness than HPV type.[16,20,21,63]

Intratypic variants of high risk HPV types have been shown to have characteristic geographical distribution patterns and to have differing pathogenic potential.[64] Intratypic variants of HPV6 and HPV11 have been also been shown to vary by geographic area, but not to be as geographically restricted.[65,66] The possible role of intratypic variants in differences in severity of respiratory papillomatosis is unclear but may be a result of combinations of

alterations in the viral genome.[64] The E5, E6 and E7 open reading frames have generally been found to be conserved across variants, suggesting that they play little role in differences in clinical behavior.[64] The activity of the long control region of the genome appears to be associated with disease aggressiveness.[64,67]

Involvement of multiple levels of the larynx or subglottis at initial laryngoscopy is associated with more severe disease.[68] On histology, while the degree of dysplasia has not been found to be associated with more severe disease, the presence of atypical mitoses and mitoses above the basal cell layer of the epithelium have been found to be associated with more severe disease.[69]

A maternal history of condyloma acuminata may be associated with aggressive RRP.[7,21,35]

Management

There is no cure and treatment consists of repeated microlaryngoscopic procedures to remove the papillomas until the patient goes into remission. Papilloma removal is either with a cupped forceps, laser (CO_2, KTP, or flash dye), microdebrider or coblation, depending on the surgeon's preference and availability of equipment.[56] In developing countries, the use of cold steel instruments to remove the papillomas is often the only means of treating these patients.[70,71] The aim of surgery is to remove the papillomas with preservation of the normal laryngeal tissue. The use of a laser or microdebrider is not associated with a longer intersurgical interval.[16] Treatment with the microdebrider results in a better voice outcome compared with the CO2 laser.[72]

Further procedures are usually at set intervals, based on an individual patient's disease severity.[56] Patients in developing countries often need to travel great distances to undergo these procedures, placing a considerable social and economic burden on the family.

Complications as a result of repeated surgical procedures are frequent and include anterior laryngeal synechiae, anterior glottic stenosis, posterior glottic stenosis and granuloma formation.[17,73,74] These complications result in abnormal vocal quality in the long term, with a greater number of surgical procedures correlating with a more pathologic voice quality.[75] Even if all visible papillomas are removed, the disease recurs as HPV DNA is found in the adjacent uninvolved laryngeal tissue as well as other adjacent anatomic sites.[18,34]

A tracheostomy may be required for patients with airway obstruction. The presence of a tracheostomy has been associated with spread of the papillomas to the trachea and lower airways,[17] but this view is controversial as it is usually patients with the most aggressive disease that undergo tracheostomy and these patients may have developed distal spread regardless of whether or not they had a tracheostomy.[56] Tracheostomies are performed more frequently in developing countries as a result of the lack of expertise to manage patients with RRP. Case series from sub-Saharan Africa have reported tracheostomy rates of 20.3% in Kenya,[46] 42–100% in Nigeria,[47–49] 47% in Mali,[50] and 50.8% in Senegal.[70] In a Bangladeshi study, 70% of patients with JoRRP required tracheostomies,[45] while studies from Thailand report a tracheostomy rate of 13.3–30%.[51,74] This is in comparison to a tracheostomy rate of 0–14% in developed countries.[13,24,28,29]

Adjuvant Treatment

A number of intralesional and systemic adjuvant treatments have been proposed for RRP, including indole-3 carbinol, mumps vaccine, MMR vaccine, HPV vaccination, interferon-α, bevacizumab, cidofovir, programmed cell death protein 1 (PD-1) inhibitors, celecoxib, and alternative treatments. Unfortunately, many of these adjuvant treatments are unavailable or unaffordable in developing countries. The highly variable nature of the disease makes determining the effectiveness of the various adjuvant treatment options difficult as natural fluctuations occur in the criteria used to determine disease severity.[59] The International Pediatric Otolaryngology Group (IPOG) recommends against the use of programmed cell death protein 1 (PD-1), colecoxib and heat shock protein E7.[56]

Intralesional therapies include cidofovir and bevacizumab. Cidofovir is a cytosine nucleotide analog that blocks the replication of DNA viruses by inhibiting viral DNA polymerase. While uncontrolled and retrospective studies have shown intralesional cidofovir to be effective for RRP with approximately 40–50% of patients achieving remission, a systematic review on adjuvant antiviral therapy for the treatment of RRP identified only one randomized double-blind, placebo-controlled trial of intralesional cidofovir administered at the time of surgical debulking with significant clinical improvements in both the cidofovir and placebo groups and no significant difference between the two groups.[76–80]

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by binding to and inhibiting the biological activity of human vascular endothelial growth factor A (VEGF-A).[81] Intralesional bevacizumab

has been shown to prolong the intersurgical interval in small case series,[81] while systemic bevacizumab has been shown to be of benefit in patients with highly aggressive disease and those with pulmonary involvement.[82,83]

Acyclovir has been found to reduce the mean surgical interval in an uncontrolled study in patients with JoRRP,[84] but there are a lack of randomized controlled trials. Although the use of both mumps vaccine and measles, mumps and rubella (MMR) vaccine have been reported in the treatment of RRP,[85,86] a randomized controlled trial did not find a significant difference in the recurrence-free remission period in patients who were treated with topical MMR vaccine as compared to those in the control group.[87]

Pepsin has been detected inside the mucosal cell cytoplasm of 45.5% of children with RRP, suggesting that laryngopharyngeal reflux may be a risk factor for JoRRP, contributing to its development by activating or reactivating latent HPV infection.[88] Patients with clinical features suggestive of GERD should therefore be treated with a H2-antagonist or proton pump inhibitor.[56]

Of the three currently available HPV vaccines, the bivalent vaccine (Cervarix®), quadrivalent vaccine (Gardasil®), and nonavalent vaccine (Gardasil® 9), two (Gardasil® and Gardasil® 9) protect against HPV6 and HPV11. In Australia, a significant decrease in the incidence of JoRRP was found following the introduction of a national vaccination program with the quadrivalent HPV vaccine, probably as a result of the maternal source of exposure to HPV6 and HPV11 being eliminated.[89] Given the higher incidence of JoRRP in developing countries, the introduction of these vaccines will likely have a greater impact of the incidence of JoRRP. Unfortunately, less than half of UN member states have introduced the HPV vaccine in their national schedule and these are mostly high income and upper middle-income countries, with most low-income and lower middle-income countries not yet having introduced the vaccine.[90] Affordability is a major barrier to the introduction of the vaccine.[90] In addition, supply is currently insufficient to fully meet the existing demand.[90]

Although these are prophylactic vaccines, they have been used as adjunctive therapy for RRP, mainly in adults. A systematic review and meta-analysis found a statistically significant reduction in the mean number of surgical procedures per month after HPV vaccination.[91] The proposed mechanisms of action include inhibition of latent HPV infection in the mucosa surrounding the surgical site by the antibody-mediated humoral immune response to the vaccine and activation of the cell-mediated response in the adaptive immune response by vaccination.

Speech Therapy

Most patients have poor voice quality that can vary from mild hoarseness to aphonia, which can persist into adulthood.[75,92] While formal voice evaluation and therapy may be of value in the management of patients,[56] these services are often not available in developing countries.[42–44]

Conclusions

JoRRP is a condition that initially presents with hoarseness but can result in life-threatening upper airway obstruction. Treatment requires repeated surgical procedures. A significant limiting factor in the early diagnosis and treatment of children with JoRRP in developing countries is the availability and accessibility of healthcare services in general, and ENT services in particular. The introduction of prophylactic vaccines that include HPV6 and HPV11 is necessary in order to reduce the incidence of JoRRP.

Disclosure

The author reports no conflicts of interest in this work.

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