JUVENILE RECURRENT RESPIRATORY PAPILLOMATOSIS:
STILL A MYSTERY DISEASE WITH DIFFICULT MANAGEMENT

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Abstract: Juvenile recurrent respiratory papillomatosis (RRP) is the most common benign neoplastic disease of the larynx in children and adolescents and has a significant impact on patients and the health care system with a cost ranging from $60,000 to $470,000 per patient. The aim of this paper is to review the current literature on RRP and summarize the recent advances. RRP is caused by human papillomavirus (HPV; mainly by types 6 and 11). Patients suffer from wart-like growths in the aerodigestive tract. The course of the disease is unpredictable. Although spontaneous remission is possible, pulmonary spread and malignant transformation have been reported. Surgical excision, including new methods like the microdebrider, aims to secure an adequate airway and improve and maintain an acceptable voice. Repeated recurrences are common and thus overenthusiastic attempts to eradicate the disease may cause serious complications. When papillomas recur, old and new adjuvant methods may be tried. In addition, recent advances in immune system research may allow us to improve our treatment modalities and prevention strategies. A new vaccine is under trial to prevent HPV infection in women; the strongest risk factor for juvenile RRP is a maternal history of genital warts (transmitted from mother to child during delivery). Better understanding of the etiology of the disease and the knowledge of all available therapies is crucial for the best management of the affected patients.

Keywords: recurrent laryngeal papillomatosis; human papillomavirus; epidemiology; management; treatment; surgical excision; adjuvant treatment

EPIDEMIOLOGY

Recurrent laryngeal papillomatosis (RRP) is a rare disease. It was first described 300 years ago and is characterized by wart-like growths in the aerodigestive tract, with predilection for the larynx. RRP has a bimodal age distribution.1 Juvenile RRP occurs in patients younger than 5 years of age, with approximately 25% of juvenile cases presenting in infancy. Adult RRP typically presents during the third decade of life.2 Juvenile RRP is more aggressive, has a more significant impact on quality of life, and accounts for greater health care costs. We will focus on this more severe form of RRP in this review.

In the pediatric population, RRP is the most common benign tumor of the larynx, afflicting 4.3 per 100,000 infants and children in the United States.3,4 Approximately 75% of affected children are the first-born, vaginally delivered infants of teenage mothers, a clinical triad that is recognized as a risk factor for the disease.5 Boys and girls are almost equally affected.6
The disease is caused by the human papillomavirus (HPV). HPV is most likely transmitted to infants during delivery through a vaginal canal harboring an active or latent infection. Silverberg et al, in a retrospective study from 1974 to 1993, examined the relationship between vaginal warts in pregnant women and the onset of RRP in their children. They concluded that the strongest risk factor for juvenile RRP is a maternal history of genital warts.

The disease, although benign, has a potentially fatal course. Excision of the laryngeal papillomas aims to prevent asphyxiation and improve voice. Despite surgical treatment, the growth of papillomas typically recurs within months or even weeks.

Children with juvenile RRP undergo repeated costly treatments—sometimes more than 100—to reduce the size of recurrent warty lesions in the upper airway. The total lifetime cost to treat 1 case of RRP is $60,000 to $470,000.

The course of RRP is variable, ranging from spontaneous remission to multiple recurrences and malignant transformation. Spontaneous remission may occur, but the age of remission is highly variable and unpredictable. Some children never enter remission and carry the disease into adulthood. Therefore, juvenile RRP, although relatively rare, has a tremendous impact on patients, their families, and the health care system.

**ETIOLOGY**

Gissmann et al and Mounts et al first demonstrated the presence of human papillomavirus (HPV) DNA in papillomas of the larynx from patients with juvenile RRP. HPV is a papova virus, icosahedrally shaped with a circular, double-stranded DNA genome surrounded by an outer capsid of protein. The HPV genome consists of approximately 7900 bp. All papilloma viruses share the same genomic organization, with all putative open reading frames (coding sequences) arranged on one DNA strand. Two of the most interesting proteins coded by HPV are E6 and E7. E6 binds to the p53 tumor suppressor gene product and stimulates abnormal cell growth by accelerating its degradation. E7 binds to the retinoblastoma tumor suppressor gene product (pRB) and blocks its growth-suppressive activity. E6 and E7 have been the subjects of extensive investigation to gain insight into the pathophysiology of juvenile RRP. More than 92 distinct types of HPV have now been characterized, and many more have been recognized.

HPVs are host specific, and each type is more or less associated with a distinct histopathologic process. HPV 6 and 11, and rarely 16 and 18, have been implicated in causing juvenile RRP. These same types are commonly associated with benign genital warts. This led to the hypothesis that juvenile RRP is transmitted from mother to child during delivery, whereas adult RRP is transmitted sexually. Protracted exposure to the virus during a prolonged second stage of labor, such as that experienced by many primigravid mothers, may lead to a higher risk of infection in firstborn children. Kashima et al suggested that newly acquired genital HPV lesions are more likely to shed virus than long-standing lesions. This may explain the higher incidence of papilloma disease observed among offspring of young mothers. However, in contrast to the low incidence of RRP, genital HPV infection is common. This means that there is insufficient evidence to support delivery by cesarean section in all women with condylomata. It is indicated that other factors may contribute to the pathogenesis of RRP. One such factor might be a host immune deficit. HPV infection is often more severe in patients with primary or secondary immunodeficiencies, although, in the majority of cases, patients do not appear to be more susceptible to other infectious agents and no consistent immune deficit has been demonstrated. Gelder et al identified a genetic association between the presence of HLA DRB1*0301 and susceptibility to juvenile RRP. The mechanism underlying this association is unknown; it will be of great interest to determine whether the presence of this allele predicts clinical severity or response to therapy in prospective studies.

Recently, gastroesophageal reflux has been implicated in RRP. Holland et al suggest antireflux treatment in patients who undergo surgery for RRP to avoid soft tissue complications such as scarring. Moreover, McKenna and Brodsky
reported a link between the presence of extr aesophageal disease and RRP. The inflammation induced by chronic acid exposure may result in the expression of HPV in susceptible tissues.

HISTOLOGY
Histologically, papillomas appear as pedunculated masses with wart-like projections of nonkeratinized stratified squamous epithelium supported by a core of highly vascularized connective tissue stroma. Cellular differentiation appears to be abnormal, with altered expression and production of keratins. The degree of atypia may be a sign of premalignant tendency.

The most common sites for juvenile RRP are the lumen vestibule, the nasopharyngeal surface of the soft palate, the midline of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricle, the undersurface of the vocal folds, the carina, and the bronchial spurs. RRP lesions occur most often at anatomical sites in which ciliated and squamous epithelium are juxtaposed to repeated trauma and replaced with nonciliated one. Papillomas may also develop in iatrogenic squamociliary junctions, for example, in tracheotomized patients.

CLINICAL DIAGNOSIS AND COURSE
Children with juvenile RRP commonly present with symptoms of an obstructed airway. The average duration of symptoms before diagnosis is reported to be longer than 13 months. Commonly, children are misdiagnosed as having asthma, croup, or chronic bronchitis. The classic triad of RRP symptoms are progressive hoarseness, stridor, and respiratory distress. Any infant or child with these symptoms may need a laryngoscopy to rule out neoplasia, with juvenile RRP being the most common. Other symptoms are persistent cough, recurrent pneumonia, dysphagia, failure to thrive, or acute life-threatening respiratory event. Differential diagnosis includes asthma, croup, and bronchitis, in addition to laryngomalacia, vascular rings, or mediastinal mass.

Because the disease is rare and frequently misdiagnosed, there is a delay in treatment. As a result, children may present with almost totally obstructed airway, and require tracheotomy to alleviate acute respiratory distress. Cole et al have suggested that tracheotomy may activate or spread the disease lower in respiratory tract. Shapiro et al noted that RRP tracheotomy patients present at a younger age and with more widespread disease, often involving the distal airway before tracheotomy. Derkay reports that tracheotomy itself can spread the disease outside of the larynx. Most of the above mentioned authors agree that tracheotomy is a procedure to be avoided unless absolutely necessary. In addition, decannulation should be considered as soon as the disease is managed effectively.

Extralaryngeal spread of respiratory papillomas has been identified in approximately 30% of children. The most frequent sites of extralaryngeal spread are the oral cavity, trachea, and bronchi.

The growth rate of papillomas is extremely variable; some patients require monthly removal of the lesions, whereas other patients with active disease require 1 or 2 annual procedures. Rabah et al showed that HPV 11 infection confers a more aggressive course of RRP. In their study, patients with HPV 11 were mostly African-Americans who were diagnosed at younger ages and tended to have longer periods of disease activity. Typing of HPV is suggested by Gerein et al at the first biopsy. Wiatrak et al reported that HPV 11 is associated with a worse outcome in infants younger than 3 years at diagnosis. Infants with HPV 11 are prone to develop more aggressive disease represented by higher severity scores, more surgical procedures per year, and likely requirement for adjuvant therapies. Poetker et al reported that a possible explanation of variable growth of papillomas may be alterations in the process of apoptosis or programmed cell death. Disruption of the balance between proapoptotic and antiapoptotic factors may affect differential cell growth and the development of neoplasms. In this paper, a significant increase in the expression of the antiapoptotic factor survivin in papilloma specimens sampled from patients with juvenile RRP was found. Dysregulation of cellular apoptosis by HPV infection could play a critical role in defining the ultimate outcome of this disease. These apoptotic mediators that are aberrantly expressed in papillomas may be novel therapeutic targets.

Williams et al demonstrated significant cross-reactivity of CD4+ T-cell responses to HPV 11 in both healthy subjects and subjects with other skin and genital HPV types. They suggest that this may aid in developing various vaccine strategies.

Rahbar et al studied the role of vascular endothelial growth factor A (VEGF-A) in RRP. It is known that VEGF-A plays an important role in
the angiogenic response, which is essential for tumor growth in a variety of human and experimental tumors. Rahbar et al report that VEGF-A is strongly expressed in the epithelium of squamous papillomas in RRP. Further investigation of growth factor expression may provide better insight into the pathogenesis and recurrence of RRP disease.

Malignant transformation of RRP to squamous cell carcinoma has been documented. There have been more than 60 single case reports in the literature of spontaneous malignant conversion of RRP to squamous-cell carcinoma. These patients generally have had long-standing, persistent disease requiring frequent surgical treatment. As already mentioned, the most common types of HPV virus are 6 and 11, but HPV 16, the more oncogenic variant, has also been shown to be present in some patients. Katz et al report a case of remote intrapulmonary spread of RRP with malignant transformation. It is not known what causes this spontaneous conversion of RRP to malignant tumor. It has been suggested that integration of HPV DNA and mutation of specific oncogenes are important for the conversion process. Oncoproteins E6 and E7 seem to be implicated. Loss of control over proliferation and cell division contributes to the development of a malignancy. Lele et al studied 4 patients with RRP who underwent malignant transformation. Only HPV 11 was identified in the examined tissue. It was also noted that increased expression of p53 and retinoblastoma (pRB) protein, combined with a reduced expression of p21 protein, appeared to be significant events associated with the progression to carcinoma. Go et al examined 7 patients with RRP who developed carcinoma. They concluded that the spontaneous transformation of RRP to squamous carcinoma is not characterized by a histologic progression through dysplasia over time. Transformation can result in the loss of HPV expression. It does not appear that p53 is a molecular marker for monitoring the transformation process. Yet much needs to be clarified.

STAGING

Although several scoring and staging systems have been proposed, clinicians have not adopted a uniformly acceptable system. Assessing the severity and clinical course of RRP disease is very important. One of the most popular staging systems is the one proposed by Colter/Derkay. This system is based on an anatomical breakdown of the aerodigestive tract into 25 subsites. The different anatomical areas are evaluated according to the presence and the severity of the disease. Physicians who are using this system can choose between different options such as 0, none; 1, surface lesion; 2, raised lesion; 3, bulky lesion. Symptoms are likewise evaluated. The summation of these scores gives a good overall evaluation of the extent of the disease, allowing for better management decisions. Clinicians have found the Colter/Derkay system to be a reliable tool because it demonstrates a high level of surgeon to surgeon reliability.

SURGICAL MANAGEMENT

Although there is no definite treatment for RRP, the most widely used treatment is surgical excision with microlaryngoscopy. The goals of any treatment modality are to secure an adequate airway, to improve and maintain an acceptable voice, and to facilitate disease remission while limiting morbidity and complications. Accomplishment of these goals is promoted by secure airway provision, careful examination of the airway, and precise removal of papillomas. Regardless of the method, care should be taken at induction of anesthesia to prevent the loss of an already compromised airway. The most common techniques used include spontaneous respiration, in which patients during anesthesia do not undergo neuromuscular paralysis, and apneic technique, in which patients undergo neuromuscular paralysis but they also get intermittent endotracheal intubation. In every case, the anesthesia team should be very experienced and skillful.

Removal of papillomas with microlaryngoscopy instruments is the oldest method, but many surgeons still prefer it because it does not burn healthy tissue, which may result in scarring and loss of vocal function. On the other hand, there is more blood loss, and there is also a possibility that blood and fragments of infected tissue can contaminate the lower airway.

CO2 laser has been a favored method of endoscopic laryngeal surgery in children since the 1970s. When used at a low power setting with an operating microscope, the laser offers precise excision, excellent hemostasis, and minimal thermal injury to underlying tissues. Disadvantages of the CO2 laser include increased operative time, increased cost, and the need for special precautions to reduce the risk of airway fire and the exposure of the staff to the virus.
Microdebrider resection of papillomas has been reported to be relatively safe and effective by Patel et al.\textsuperscript{41} Patel et al\textsuperscript{42} have found that total surgical time, including preparation time, to be shorter for microdebrider resection than for CO\textsubscript{2} laser resection of papillomas in children. Pasquale et al\textsuperscript{43} reported that patients who underwent microdebrider excision had quicker improvement in voice quality, shorter procedure times, and lower overall procedural costs compared to patients who underwent CO\textsubscript{2} laser treatment. Microdebrider resection of papillomas avoids the risk of airway fire. Less postoperative pain after treatment using the microdebrider has been reported anecdotally by the parents of children with juvenile RRP.\textsuperscript{42–44}

Recently, pulse dye laser excision has been recommended as a method of treatment. Franco et al\textsuperscript{45} reported that this laser type, which is primarily for treatment of vascular lesions, is relatively effective and safe for the treatment of RRP. However, this method seems less effective for large papillomas.

The most common complications of all surgical treatment modalities include scarring, webbing, and alteration of the mucosal wave. Because reliable eradication of juvenile HPV is impossible, it is wise to leave minimal amounts of papillomas at sites where irreparable scarring may occur, especially at the anterior commissure and the posterior glottis. More rare complications include airway stenosis, airway perforation, hemorrhage, and airway fire.

**ADJUVANT METHODS OF MANAGEMENT**

Although surgical management remains the main therapy for juvenile RRP, ultimately, many of the patients with the disease require some form of adjuvant therapy. The most widely adopted criteria for initiating adjuvant therapy are a requirement for more than 4 surgical procedures per year, distal multisite spread of disease, and rapid regrowth of papilloma disease with airway compromise.\textsuperscript{37} Approximately 10% of the patients with juvenile RRP need adjuvant treatment.\textsuperscript{37} The most commonly recommended adjuvant therapy is $\alpha$-interferon.\textsuperscript{8}

$\alpha$-interferon is a group of proteins produced by leukocytes in response to viral stimulation. It is a biologic response modifier that stimulates existing host defenses into an antiviral state, modulates immune responses, inhibits cell growth, and induces several enzyme systems.\textsuperscript{37} Recombinant $\alpha$-interferon is currently used. Responsiveness of juvenile RRP to $\alpha$-interferon has been demonstrated in several studies. Szeps et al\textsuperscript{46} report in their study of a heterogeneous group of patients that there was a tendency that cases of HPV 6 to respond better to $\alpha$-interferon to HPV 11 or HPV negative cases. In the same paper they mention that there was no significant difference in viral load and hyperproliferative state of the HPV-affected epithelium post-treatment in patients who responded well to $\alpha$-interferon. Gerein et al\textsuperscript{27} reveal maximal effectiveness of $\alpha$-interferon treatment in a 20-year follow-up of RRP patients. They also suggest HPV typing in RRP patients after the first biopsy due to worse prognosis with HPV 11. Side effects include flu-like syndrome, leucopenia, coagulopathy, alopecia, and neurological complications. $\alpha$-interferon is administered intramuscularly, intravenously, or subcutaneously. The dose is increased gradually to a target of 3 MU/m\textsuperscript{2} body surface daily for a month, and then the dose is reduced to 3 times/week for at least 6 months. Afterward, the dose may be slowly tapered or reintroduced in those children with recurrence. The role of intralesion injection of interferon is under investigation.

Indole-3-carbinol (I-3-C) is a derivative of cruciferous vegetables. The ability of I-3-C to slow papilloma growth is believed to be caused by its influence on estradiol metabolism. By altering the site of estradiol hydroxylation, I-3-C decreases the production of 16a-hydroxyestrone and increases the production of 2-hydroxyestrone. In breast tumors, the former estradiol derivative has a proliferative effect, while the latter has an antiproliferative effect.\textsuperscript{47} I-3-C is best administered as a dietary supplement because the quantity present in cruciferous vegetables is highly variable and unpredictable. The proposed dose for children weighing less than 25 kg is 100 to 200 mg daily. It is well tolerated. Side effects that have been reported are dizziness and headache.\textsuperscript{34} The recent study of Rosen and Bryson\textsuperscript{48} of long-term results of I-3-C treatment for RRP argued that it is a safe and efficacious treatment because 70\% of their patients had complete or partial response to it. Pediatric patients as well as adults, in this same study, did not respond to I-3-C, implying that juvenile form of the disease is more aggressive. Further studies are needed.

Cidofovir is a cytosine nucleotide analog that has been shown to have potent antiviral activity against a broad spectrum of herpes viruses. Its mechanism of action is through the active intra-
cellular metabolite cidofovir dihydrate, which inhibits cytomegalovirus DNA polymerase. Cidofovir dehydrate has an intracellular half-life between 17 and 65 hours, which permits continuous antiviral efficacy with infrequent dosing. The cidofovir injection is performed under general anesthesia using spontaneous ventilation. The cidofovir injection is administered at the maximum dose of 1 mg/kg every 2 to 3 weeks.49,50 Cidofovir can be toxic. Animal studies have identified nephrotoxicity, which appears to be related to dosage. Neutropenia has also been reported. The results of cidofovir use are promising and offer hope to those who are most severely affected with juvenile RRP. Pransky et al51 in a study of 10 children reported that patients with severe RRP showed good response with intranasal cidofovir treatment, but it is necessary for safety profiles to be established. Recently, a case report of intravenous administration of cidofovir in an 8-year-old has been reported.62 The patient had lung lesions that completely resolved with local and intravenous cidofovir plus I-3-C treatment. A review of cidofovir treatment by Shehab et al53 concludes that long-term risks associated with cidofovir remain to be seen and that further studies are necessary to determine the most appropriate dose, frequency, and duration of therapy.

Acyclovir is an acyclic purine nucleoside analog. When acyclovir metabolites are incorporated into DNA, they cause breaks in the DNA strand. The exact mechanism of acyclovir’s function in juvenile RRP is uncertain but may be related to coinfection with a member of the herpes virus family.37 Side effects are rare and include nausea, vomiting, diarrhea, fatigue, and dull headache. Liver function is monitored at the beginning of therapy and every 8 weeks. The beneficial effect of acyclovir is not well documented.54,55

Photodynamic therapy is based on the selective uptake of hematoporphyrins by neoplastic cells, including papillomas.56 A photosensitizing factor is administered intravenously, and after 6 days, activation of the factor is accomplished by red light laser. Some studies have shown a decrease in the rate of papillomas recurrence.57 Shikowitz et al58 reported that RRP patients who underwent photodynamic treatment with mTHPC as a photosensitizer showed improvement of their disease, possibly through an immune response, but remission was not permanent.

Mumps is a viral illness against which most children are immunized at around 1 year of age (MMR vaccine). In 1980, it was suggested that the mumps virus and human papillomavirus might have similarities that could translate into papilloma treatment by simple immunization using mumps vaccine. Local infiltration of mumps vaccine, when combined with serial, prospective laser excision of respiratory papillomas to maintain airway and maximize voice, has been found capable of improving the emission rate.59 It is reported that mumps vaccine can be administered intranasally more than once in the same site. Pashley states that it is safe, readily available, and easy to use.59 It is not clear how this occurs and certainly needs further investigation by other studies to confirm these results. Moreover, Lieu and Molter60 stated that high doses of mumps vaccine may be not without risks.

Gene therapy may be an important key in the treatment of juvenile RRP. Sethi and Palefsky61 designed an HPV specific therapy using the herpes simplex virus type 1 thymidine kinase gene. They transferred this gene into HPV 16 infected cells expressing E2 protein. Treatment of these cells with either ganciclovir or acyclovir resulted in cell death. They suggested that this may be a clinically feasible therapeutic strategy. Recently, therapeutic vaccination has gained great interest.62 By reinforcing the immune system, better control of the disease can be achieved. A candidate therapeutic vaccine, named HspE7, has completed phase II testing in juvenile RRP patients.63 It consists of a recombinant fusion protein (heat shock protein Hsp65 of Mycobacterium bovis var.) expressed in E. coli. A confirmatory phase III study of this vaccine is under development.

**PREVENTION**

Given the challenges in managing juvenile RRP, the most important measure is prevention of RRP. It is well established that maternal infection with HPV is a risk factor for juvenile RRP. Unfortunately, the mechanism of transmission is not absolutely clear. This makes management uncertain. The proposed cesarean section is not a widely accepted way to prevent neonatal HPV infection for various reasons.64 Perhaps the solution to the juvenile RRP problem would be the prevention of genital HPV infections.65 Vaccines designed to prevent specific types are currently under development.66 A quadrivalent HPV vaccine (against types 6, 11, 16, and 18) has the broadest coverage, while other vaccines target fewer types.66 Recent accomplishments in developing vaccines based
upon virus-like particle technology have brought this possibility close to reality in coming years.67

CONCLUSION
Overall, juvenile RRP is a relatively rare disease. This has had a negative impact on the systematic evaluation of treatment modalities by scientists. Patients may have a poor quality of life due to multiple recurrences of airway obstruction or altered vocal quality. Treatments may be numerous and costly, with devastating results for patients and their families. Recent advances in surgical excision of the papillomas have improved the safe maintenance of the airway and offer an acceptable voice to the patients. However, overenthusiastic surgical management attempting to eradicate the disease may cause serious complications. Adjuvant medications have reduced the frequency of surgical excisions and hospitalization, but it seems that none of the adjuvants can eradicate the disease. There are still missing data regarding the HPV virus and the pathogenesis of juvenile RRP. Ongoing studies may give the answer to the missing links, and thus prevention, early diagnosis, and effective management may be a reality in the near future.

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