

## Transmission and prevention of recurrent respiratory papillomatosis

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**Abstract:** Recurrent respiratory papillomatosis (RRP) is caused by Herpes papilloma virus (HPV) infection of the throat. RRP is categorized into juvenile-onset (JORRP) and adult-onset (AORRP) based on diagnosis before or 12 years of age respectively. The incidence rate of RRP a disease of larynx estimated to be 4.3 per 100,000/year for juvenile-onset and 1.8 per 100,000/year for adult-onset. The disease has been observed in patients during postnatal period and in patients as old as 84 years. Respiratory papillomatosis is the most common benign neoplasm of the larynx in children with tendency to recur and spread to the respiratory tract. Rapid growth of lesions often necessitates surgical incision to avoid asphyxiation. Children are frequently misdiagnosed as asthma, bronchitis or croup. Diagnosis is by laryngoscope and biopsy for HPV. Treatment commonly by surgery, carbon dioxide laser surgery and photodynamic therapy to control tumors. Many antiviral drugs like cidofovir have been used. Highly effective and safe treatment is not yet available, current therapies not designed to eradicate HPV infection rather to eliminate clinical manifestations. New approaches are directed at molecular viral targets and immunomodulation.

**Keywords:** Recurrent respiratory papillomatosis, Human papilloma virus, Transmission, and Prevention

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### I. Introduction

Recurrent respiratory papillomatosis (RRP) also known as laryngeal papillomatosis or glottal papillomatosis or associated with condyloma acuminata is a rare medical condition 2 per 100,000 adults and 4.5 per 100,000 children [1], caused by an Herpes papilloma virus (HPV) infection of throat [2]. HPV infections can occur at any portion of the aero digestive tract, although it is most extensively described in the larynx and trachea in the form of RRP. RRP was first described in the late 1800s by Sir Morell Mackenzie who recognized papilloma's as a distinct lesion of larynx in children [3]. It was not until the advent of modern molecular genetic techniques in the 1990s that HPV was confirmed as the causative agent of RRP. Of more than 100 serotypes of HPV, types 6 and 11 are most common [4]. RRP is categorized into juvenile-onset (JORRP) and adult (AORRP) based on diagnosis before or 12 years of age, respectively. The disease has been observed in patients during immediate postnatal period and in patients as old as 84 years [5]. The incidence rate of RRP which is primarily a disease of the larynx, is estimated to be 4.3 per 100,000/year for juvenile-onset form of disease and 1.8 per 100,000/year for adult onset form [6]. Prevalence rates are about 2 fold to 9 fold [6]. In a Danish study incorporating 50% of the population of the country, the overall incidence of RRP was 3.84 cases per 100,000, with children rate at 3.62 per 100,000, while adult-onset occurred at a rate of 3.94 per 100,000 [7, AD, 12]. The average life time economic burden to treat one patient in the United States with RRP has been estimated at \$60,000-\$470,000 [8]. Symptoms include changes in voice, stridor is the second most common symptom, first respiratory and then diphasic. Less common presenting symptoms include chronic cough, recurrent pneumonia, failure to thrive, dyspnea, dysphagia, or acute respiratory distress, especially in infants with upper respiratory infection [9]. Younger age at diagnosis is associated with more aggressive disease and the need for more frequent surgical procedures to decrease the respiratory burden [9]. Many antiviral drugs like cidofovir have been used to treat RRP, but none completely stops the tumors from growing. Adjunct therapy with interferon may be used in severe cases [10]. The potential for a quadrivalent human papilloma vaccine is being explored to reduce the incidence of disease [9]. The paper reviews the current literature, transmission and prevention of RRP.

### II. Epidemiology

RRP is categorized into juvenile-onset (JORRP) and adult-onset (AORRP) [5]. Juvenile-onset is most commonly diagnosed between 2 and 4 years of age with dysphonia being the most common presenting complaint [11]. The majority of JORRP patients (75%) have been diagnosed by 5 years of age. Children who are diagnosed at a younger age have a higher risk of disease progression compared with children diagnosed later in life [12]. Studies have shown no sex predilection among children with RRP. Adult-onset RRP presents at ages 20 to 40 years, with 4:1 male female ratio [13]. Anecdotal observations suggest that most pediatrics are first born,

have young primagravid mothers, and come from families of low socioeconomic status[5]. Numerous studies have been performed to elucidate the true incidence of RRP. Recently, Campisi created a national database incorporating all children (less than 14 years old) with RRP in Canada treated by Pediatric Otolaryngologists. This study found the national incidence of RRP from 1994-to 2007 to be 0.24 per 100,000 with a prevalence of 1.11 per 100,000[14]. These estimates are significantly lower than in several previous studies, but similar to a population based study of RRP patients in Seattle and Atlanta [15].

Other researchers attribute this discrepancy to either overestimations by other studies based on extrapolated data or higher incidence in other countries[9]. Danish study reported overall incidence of RRP was 3.84 cases per 100,000, among children incidence was 3.62 per 100,000 and adult-onset cases at a rate of 3.94 per 100,000[7]. These numbers were comparable to those found in a U.S. study in which the incidence of RRP in the pediatric population to be 4.3 per 100,000 and in adult population to be 100,000[5]. A recent pilot study of a large database of publically and privately insured patients in the United States consistently showed RRP incidence was higher in publically insured patient compared with private insurance (3.21 vs 1.98 per 100,000, respectively)[8]. The explanation this may be that patients with public insurance tend to come from a lower socioeconomic level than those with private insurance. A cross-sectional study of all active JORRP patients from the hospital for sick children in Toronto showed that nearly half of these patients were below the poverty line in Canada[16]. This study however, did not show no correlation between socioeconomic status and severity of disease[16].

RRP places a large economic burden on individual patients and their families as well as society as a whole. On average, a child presenting to an academic center in the United States with RRP requires 19.7 procedures over their lifetime, with a mean frequency of procedures being 4.4 per year[17]. Approximately equal numbers of adults and children with RRP (17% vs 19%, respectively) will have aggressive disease requiring more than 40 lifetime procedures. With an average cost one patient with RRP being \$60,000 to \$470,000[[8].

Three types of HPV infections are widespread throughout the general population[18]. Common warts, which represents up to 71% of all cutaneous warts, occur frequently among school-aged children, with prevalence rates of 4% to 20%[19]. Other groups at high risk for the development of cutaneous warts include butchers, meat packers, and fish handlers[20]. An approximately 6.2 million genital HPV infections occurred in the age group 15 years to 44 years in the United States in 2000[21]. These infections are the most commonly acquired viral sexually transmitted infection (STIs). Three fifths of these were high-risk types for cervical neoplasms. Most of the sexually active population is likely to be infected in a lifetime[22,23]. The prevalence rate of condyloma acuminatum (plural, condylomata acuminata), or anogenital warts (venereal warts), in the general population is approximately 1% [23]. HPV infection of the cervix gives rise to the most common cause of squamous cell abnormalities on Papanicolaou (Pap) smears[24].

### **III. Transmission**

Close personal contact is assumed to be important for transmission of most cutaneous warts although strong epidemiologic evidence for this assumption is lacking [20]. Evidence that anogenital warts are sexually transmitted includes the observations that the age of onset is similar to that in other sexually transmitted disease (STDs) and that disease develops in approximately two thirds of the sexual contacts of patients with anogenital warts [25]. Despite these observations in adults, young children may acquire genital warts from hand contacts with nongenital lesions[26].

The near universality of HPV in humans has been well documented. By far the largest reservoir of this virus, especially for types 6, 11, 16, and 18, is the anogenital tract. It is from this source that HPV infections of the respiratory tract are believed to originate [9]. Human papilloma virus infection of anogenital tract is the most common sexually transmitted infections in humans. The prevalence of clinically apparent genital papilloma is in approximately 1% of the population [27]. The exact mode of transmission in RRP remain elusive and is likely variable depending on the age of the patient at presentation. Several retrospective and prospective studies have that HPV may be passed by vertical transmission from mother to child [28]. 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 [9].

Silverberg et al showed that children born to mothers with active condylomata had 231-fold increased risk of developing RRP when compared with children born to disease free mothers[29]. In addition they, also showed that children born to women with active condylomata had twofold higher risk of developing RRP if labor lasted more than 10 h. Kashima et al found that childhood-onset RRP patients were more likely to be first-born and vaginally delivered than control patients of similar age[30]. Larson and colleagues hypothesized that primagravid mothers are more likely to have a long labor second stage of labor and that prolonged exposure to HPV in birth canal leads to a higher risk of infection in the first-born child. They also suggested that newly acquired HPV lesions are more likely to shed virus than long-standing lesions. This would explain the higher

incidence RRP observed among the offspring of young mother of low socioeconomic status-the same group that is more likely to acquire sexually transmitted infections such as HPV [9].

Hallden and associates showed that 54% of JORRP patients were born to mothers with history of vulvar condylomata at time of delivery [31]. Despite these apparent close association, few children exposed to genital warts at birth actually develop clinical disease [32]. It is not well understood why RRP develops in so few children whose mothers have condylomata. Although HPV could be recovered from the nasopharyngeal secretions of 30% of infants exposed to HPV in the birth canal, the number of infants expected to manifest evidence of RRP is only a small fraction of this [33]. Reports of neonatal papillomatosis suggest that, in at least some cases, development of the disease may occur in utero. As caesarean section does not seem to prevent of RRP in all cases, a better understanding of the risk factors associated with RRP is needed before the efficacy of caesarean delivery in prevention papilloma disease can be fully assessed [34].

Patients with AORRP, a case control report study found them more likely to have more lifetime sexual partners and a higher frequency of oral sex than those reported in adult controls [30]. These data would suggest that patients with AORRP are exposed later in life than patients with JORRP. However, HPV has the disturbing capability to form latent infections in the basal layer of otherwise healthy appearing mucosa [35]. It has been suggested that AORRP may represent a reactivation of HPV infection acquired during birth instead of a de novo exposure during adulthood [9]. Neonates are more likely to harbor HPV DNA in the oral cavity if the cervix of the mother contains HPV DNA [5]. Family members and others with close personal contact with these patients are not at risk for development of the disease [5]. The role of fomites in the transmission of HPV infection is uncertain. However, nosocomial transmission appears possible because infectious virus can be recovered from the fumes released from lesions during treatment with carbon dioxide laser or electro coagulation [36]. In addition, HPVs are resistant to heat, and use of an autoclave is probably necessary for sterilization of contaminated instruments [37].

#### **Papillomavirus and its association with malignancy**

The oncogenic potential of animal papillomaviruses was shown many years ago [38]. The low prevalence of cancer of the uterine cervix among Catholic nuns [39], the direct association of risk with number of sexual partners, and the increased risk of the malignant disease that is associated with a male sexual partner whose previous consort had cervical cancer have been observations consistent with sexually transmitted agent playing a role in the pathogenesis of cervical cancer [40]. The association between those HPV types called high risk oncogenic and cervical cancer is strong, with odds ratio that range from 50 to 100 fold. For those oncogenic of these viruses, HPV-16 for squamous cell carcinoma (SCC) and HPV-18 for adenocarcinoma, the odds ratios range from 100 to 900. In a worldwide survey, HPV DNA was found in 99.7% of cervical samples [41].

#### **IV. Pathogenesis**

The pathogenesis of HPV has been reviewed by several authors [42]. The incubation period was established experimentally with inoculation of human subjects with extracts of cutaneous warts [43]. Most often, warts developed within 3 to 4 months although lesions occasionally grew as early as 6 weeks or as long as 2 years after inoculation. A similar incubation period was observed for genital warts among wives of American soldiers returning from Korean war [44]. Little is known about the first stage of HPV infection, the virus replicative cycle is assumed to begin with the entry of particles into stratum germinativum (Basale) because viral DNA is detected in the nuclei of basal cells [45]. As the basal cells differentiate and progress to the surface of the epithelium HPV DNA replicates and is transcribed, and viral particles are assembled in the nucleus. Ultimately, complete virions are released, probably still tightly associated with the remnants of the shed dead keratinocyte shell [46]. Some infected cells undergo the characteristic transformation of koilocytosis. With histology, koilocytes (from Greek Koilo "cavity").

Host defense responses to HPV infection are poorly understood. Nevertheless, several clinical observations suggest that an effective immune system is important in the resolution of HPV infection. HPV diseases occur frequently and are often severe in patients with both primary and secondary immunodeficiency's (e.g., Wiskott-Aldrich syndrome, common variable immunodeficiency) [47]. A humoral and cellular immune response does develop after HPV infection, but its laboratory correlates are not necessarily uniform or constant. The E7 and L1 proteins are the strongest antigens [48].

#### **V. Clinical manifestations**

Recurrent respiratory papillomatosis is the most common benign neoplasm of the larynx in children. Despite its benign histology, RRP has potential morbid consequences and is often difficult to treat because of its tendency to recur and spread throughout the respiratory tract [49]. RRP has been described by several authors [6]. Patients present with hoarseness or, in infants, with an altered cry. Sometimes these symptoms are accompanied by respiratory distress or stridor. The disease may be spread to the trachea and lungs and lead to

obstruction, infection, and respiratory failure. In young children, rapid growth of lesions often threatens the upper respiratory tract and frequently necessitates surgical incision to avoid asphyxiation. Children are frequently misdiagnosed as having other airway problems such as asthma, bronchitis, or croup [13]. In adults; the course of disease is usually less aggressive. Lesions may however, undergo malignant transformation, particularly in patients who have received radiation therapy or in cases with lung involvement [6].

## **VI. Diagnosis**

The diagnosis of laryngeal papillomatosis is done by placing a mirror into patient's mouth to reflect light onto the vocal cords and examining the larynx. More often, a doctor or a trained speech-language pathologist diagnoses laryngeal papillomatosis by an indirect laryngoscope in the office. This procedure involves the placement of a flexible, fiber optic camera through the patient's nose to view the vocal folds in the throat or use a straight, rigid camera placed through the mouth to view the vocal folds [50]. The most accurate way to diagnose laryngeal papillomatosis is for a biopsy to be conducted and for the lesion to be tested for HPV. This procedure takes place in an operating room with the patient under general anesthesia. This is sometimes the best option for small children. This disease is often misdiagnosed as asthma, croup or chronic bronchitis [51]. The consequences may be serious, as papillomas are least partially obstructing the airway to cause these symptoms and should be removed immediately [50]. Coope and colleagues suggest that attending physician must ask about hoarseness of voice in a history of any child presenting with cough or asthma-like symptoms [52].

Hoarseness in adults may be caused by vocal fold nodules, reflux laryngitis, vocal fold cysts or polyps, leukoplakia, vocal fold neoplasms, sulcus vocalis, inflammatory laryngitis (e.g., tobacco abuse, steroids inhalers), vocal fold immobility, hypothyroidism, systemic illness such as sarcoidosis or amyloidosis [13].

**Imaging** Has limited use, except in assessing for other issues causing airway compromise in children or assessing distal pulmonary papillomatosis. High kilo voltage plain film or airway fluoroscopy may be helpful in this regard but not specifically assist in the diagnosis of RRP [13].

**Laboratory workup.** No specific laboratory tests are helpful in RRP. Some otolaryngologist recommend HPV-typing at time of resection. This does not alter treatment but can offer some prognostic information, as HPV-11 patients tend to have more aggressive disease, more recurrences, more surgical procedures, and more use of adjuvant therapies [13].

## **VII. Treatment**

Traditional surgery and carbon dioxide laser surgery, a "no touch" removal of affected tissue, are forms of treatment for laryngeal papillomatosis. Carbon dioxide laser removal is the most common removal method [51]. The carbon dioxide laser must be used precisely to prevent scarring, fibrosis, and laryngeal web malformation. In children, carbon dioxide laser is effective for removing papillomas on the larynx. Photodynamic therapy controls tumors by using targeted dyes and bright light to illuminate tumors [1]. In this procedure, a physician injects a light sensitive dye that is only absorbed by the tumors. Then the physician activates the dye using a bright light, and the tumors are eliminated. This procedure has also been able to decrease the number of tumors that reoccur [1]. Another method is tracheotomy, which reroutes air around the affected area. An incision is made in the front of the patient's neck, and breathing tube is inserted through a hole (stoma) into the windpipe. The patient is then able to breathe through the tube. Although this is usually temporary, some patients may use tube indefinitely [1]. This method should be avoided if at all possible, since insertion of a breathing tube may cause the tumors to form as far down as lungs [51].

Many antiviral drugs like cidofovir have been used to treat laryngeal papillomatosis, but none completely stops the tumors from growing. Most antiviral are injected to control the frequency of tumor growth. The efficacy of the same is debated and subject to research. Some side effects of antiviral include dizziness, headaches, body aches. Adjuvant chemotherapy with interferon may be used in severe cases. Regardless of the treatment used, the tumors may occur once or twice a year. In addition, speech therapy may be beneficial to assist with vocal hygiene and retaining of voice [10].

Highly effective and safe treatments for HPV diseases are not yet available, and the current therapies are not designed to eradicate HPV infection. Rather, their purpose is to decrease or, if possible, eliminate clinical manifestations. The current therapeutic armamentarium has been largely developed empirically over decades and too often relies on the physical or chemical destruction of lesions. New approaches are directed at molecular viral targets and immunomodulation [53].

## **VIII. Prevention**

Intuitively caesarean section would seem to reduce the risk of vertical transmission of HPV. However, this procedure is associated with a higher morbidity and mortality for the mother and much higher economic cost than elective vaginally delivery. Shah and colleagues estimated that the risk of child contracting the disease from a mother who has active condylomata and delivers vaginally is only 1 in 400 [34]. The characteristics that

differentiate this one child in from the other 399, remain unknown. Given the uncertainty surrounding intra-partum exposure, there is presently insufficient evidence to support delivery by caesarean section in all pregnant women with condylomata[54]. However, there may be some benefit in managing condylomata during pregnancy if it can be accomplished without increasing the miscarriage rate. Discussion between the at-risk mother and her obstetrician regarding the issue of HPV transmission would seem appropriate [9].

The major development in the field of HPV diseases has been the availability since 2006 of an FDA approved vaccine for the prevention of several genital HPV diseases, including cervical cancer, Gardasil (Merck, WestPoint, PA), is directed against HPV types 6, 11, and 18, thus aiming at 80% to 90% of the agents of genital warts and 70% of the agents of cervical cancer. It is made with the expression in baker's yeast of the L1 gene of these genotypes[55]. The vaccine is contraindicated in subjects allergic to yeast (*Saccharomyces cerevisiae*) or who have had a prior allergic reaction to the vaccine or its components[56]. In the primary target population ages 11 to 12 years[57]. Based upon the clinical studies, the vaccine is predicted to reduce the incidence, morbidity, and mortality of cervicovaginal HPV disease. An added, and often overlooked, benefit may be concomitant decrease in the incidence of RRP in all age groups. In addition, there may a reduction in 20-25% of head and neck squamous cell carcinomas attributed to HPV [58]. Larson and colleagues contend that universal vaccination with the quadrivalent vaccine could lead to the elimination of the maternal and paternal reservoir of HPV and lead to a near eradication of RRP caused by HPV types 6 and 11[9].

## IX. Conclusion

Recurrent respiratory papillomatosis is a benign neoplasm disease of larynx caused by papillomavirus. Early diagnosis and treatment should be considered. HPV quadrivalent vaccine for the prevention of several genital HPV diseases is directed against HPV types 6, 11, and 18. Vaccine is recommended for the population ages 11 to 12 years to reduce morbidity, and mortality in HPV disease. Vaccine may also eradicate RRP caused by HPV types 6, and 11.

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