

Exploring Recurrent Respiratory Papillomatosis: A Mini-Review



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Abstract

Recurrent respiratory papillomatosis (RRP) is a term which has been used to describe Human papillomavirus (HPV) infection of the upper aerodigestive tract affecting both children and adults. It's mostly self-limited and with bimodal distribution pattern in children. The juvenile form develops in patients less than 20 years of age, but adult form develops after 20 years of age in those at their 3rd or 4th decades of life. Though the virus has affinity to any part of the upper aerodigestive tract, but it has much more propensity to the larynx. Most infections in children occur at birth during passage through the birth canals of contaminated mothers while in adults, HPV is transmitted sexually. Natural history of RRP has remained unpredictable ranging from mild attacks with spontaneous remissions to severe attacks manifested by its aggressiveness characterized by distal spread to the pulmonary tree and recurrent episodes which necessitate frequent surgical debulking. RRP usually present with nonspecific symptoms of airway involvement, including chronic cough, hoarseness, wheezing, stridor, and chronic dyspnea and thus commonly misdiagnosed. Recurrent attacks of RRP impair one's quality of life such as impaired academic performance and altered socio-economic status in both children and adults due to social stigma which may be due to hoarseness of voice and/or tracheostomy. Although rare, RRP can undergo malignant transformation to squamous cell carcinoma. Such transformation has remained to be a topic of debate since it has been reported invariably. The aim of this review is thus to discuss various aspects of RRP.

Keywords: Recurrent; Respiratory; Papillomatosis

Introduction

Recurrent Respiratory Papillomatosis is a rare disease characterized by recurrent growth of benign papillomatous lesions in the respiratory tree of both adults and children with the exclusive aetiology being Human papillomavirus [1-4]. Such lesions may occur anywhere in the upper aerodigestive tract [5] though in most occasions affect the larynx and that's why some literatures describe such disease condition to be "Recurrent laryngeal papillomatosis". It has the tendency of afflicting both children and adults [6,7]. The average time from onset of the symptoms and diagnosis ranges from 1 to 8 years [4]. The papillomata can occur anywhere in the aerodigestive tract but most frequently in the larynx, affecting both children and adults [5]. Even though the disease is benign but may cause significant morbidity and mortality and an accompanied excess expenses incurred in treating the patient who usually undergo numerous episodes of surgical interventions that are preceded by frequent doctor visits for the same complaints. There are some reports showing the possibility of malignant

transformation of RRP, but this has been invariably reported [8,9]. The estimated incidence of RRP is 2 per 100,000 in adults and 4 per 100,000 in children [4,10]. The prevalence of HPV infection has been increasing gradually in the female population where the estimated prevalence in women aged 14-59 is 26.8%, and that in women aged 20-24 years is 45%. As per the socio-economic status, the incidence of RRP varies invariably where they are higher in groups with lower socio-economic status and low educational levels though no correlation has been found between socioeconomic status and the severity of RRP [11].

Executing management to patients with RRP has remained to be a challenge to Otorhinolaryngologists. There are promising surgical interventions coupled with several adjuvant therapies, but they will still remain to be palliative measures to such terrible disease [12-18]. Intraoperatively, surgeons have been facing challenge when it comes to voice preservation techniques during microlaryngeal surgery especially when repeated surgeries for the papillomatous lesions are to be

performed. In developing countries where patients are living in sub-standards of life and with poor tendency of seeking health care, they may present with upper airway obstruction secondary to obstructive lesions at the upper aerodigestive tract necessitating tracheostomy first before surgical removal of the papillomatous lesions. Social life after tracheostomy has been challenging to sufferers due to some acts of social isolation. Provisional diagnosis may be made based on thorough history taking, physical examination and at times imaging findings; the final diagnosis is based on histopathological analysis of biopsy specimens from the anatomical site involved, collected upon direct laryngoscopy [19]. Findings from the available literatures have been reported invariably and the aim of this paper is thus to give an overview on aetiology, clinical presentation, treatment and outcomes of RRP.

Aetiology, Age at Presentation, Risk Factors and Severity Course of Recurrent Respiratory Papillomatosis (RRP)

RRP has been reported consistently to be caused by low risk HPV subtypes which are HPV type 6 and 11. Both subtypes are implicated in both Adult and Juvenile onset forms of RRP. HPV is a DNA virus of the Papillomaviridae family and has non-encapsulated, double-chain icosahedric structure, and is composed of 72 capsomeres which are approximately 55 nm in diameter [20,21]. Generally, there are more than 100 subtypes of HPV [4,15,22-24]. Majority of the available studies report the mean age at diagnosis of Juvenile Onset RRP to be 3.8 years while the adult form manifests normally in the 3rd or 4th decade of life and rarely manifests in those older than 60 years of age and the younger the patient's age at diagnosis, the more likely the patient will have severe disease [1,11,25]. The disease associated with HPV-11 is more severe and thus as many as about 70% require tracheostomy compared to 20% of those children afflicted with HPV-6 [1,3,26,27]. Most patients with RRP caused by HPV-11 runs a severe course of disease and thus may require several surgical interventions [26-29]. Other subtypes, such as 16,18, 31, and 33, are also associated with RRP, although with reported lower prevalence. Subtypes 16 and 18 are considered to be high risk, with the potential for malignant transformation, particularly to squamous cell carcinoma, which occurs in less than 1% of juvenile RRP cases [20,30]. With the HPV subtype reported consistently to cause the severe form of RRP, there are other characteristics belonging to the virus such as spread outside the larynx, longer duration of the illness, propensity for malignant transformation especially in adults and the tendency to require high annual number of surgeries and lower age at which the diagnosis is made [31-36].

The Juvenile form of RRP tends to be more aggressive and with numerous papillomatous lesions and high recurrence rate and thus require many surgical interventions during one's life time to maintain airway and thus the risk of voice compromise is commoner with this form [27,35]. The cause of Juvenile form

is peripartum transmission of the implicated virus and even though vaginal delivery is implicated but caesarian section is also not protective [36-38]. The known classic triad for the increased risk of the Juvenile form include being first born and vaginal delivery by a teenage mother (mother younger than 20 years) of lower socio-economic status. Sexual abuse to children younger than 5 years have also been reported in some occasions [38]. It has been postulated that newborns can acquire RRP from genital HPV infection during passage through an HPV-infected birth canal as a result of transplacental transmission of maternal infection or postnatal contact with an infected individual [8]. The risk is thought to be higher in women with overt anogenital warts or disease from a recent HPV infection at the time of delivery [1]. With the Adult form of RRP, sexual transmission is the most probable risk factor, and this may be linked to increased number of life time sexual partners and more frequent acts of orogenital sex [38]. In this form, the papillomas are often solitary and with a high degree of inflammatory reactivity thus they do not usually spread and recur less frequently than those seen in the juvenile form [30].

Affinity of HPV to Epithelial Surfaces of the Respiratory Tree especially the Larynx

The virus implicated in RRP has shown predilection to the stratified epithelium belonging either to mucosal or even cutaneous surfaces and upon stem cell infection particularly keratinocyte within the basal layer of the mucosa of the airways tends to induce laryngeal papillomatosis [39]. The typical anatomical location where such process begins is at various anatomical sites where squamous epithelium becomes adjacent to ciliated columnar epithelium at the respiratory tree [40]. Consequent to activation of HPV epidermal growth factor receptor (EGFR) pathway and inactivation of several tumor-suppressor proteins, cellular proliferation and defective epithelial differentiation ensues in affected individuals [39]. As a result of the stated mechanisms directed to the mucosal surface of the respiratory tree, exophytic growths characterizing laryngeal papilloma's develop [5].

Sex Distribution of Recurrent Respiratory Papillomatosis

Available literatures have shown diverse results in terms of sex predilection in RRP. Most studies have concluded Juvenile Onset RRP to affect males and females in equal predominance but the Adult Onset RRP affects males than females [1-4]. A different picture is depicted in the adult form of RRP where males are more affected than females. Whether males are more exposed to orogenital sex than females remain to be still uncertain, but this may be a hypothesis since the adult form may develop from a latent infection which was acquired since childhood.

Clinical Presentation of RRP

Available studies have reported patients with RRP to have variable clinical features though symptoms of airway involvement

like progressive hoarseness, stridor, dyspnea, wheezing acute respiratory distress or chronic cough should alarm about the possibility of RRP. Because of non-specific features of RRP, a high index of suspicion is needed whenever a clinician encounter a child presenting with such suggestive symptoms otherwise experience from hospital settings shows misdiagnosis of patients presenting with such complaints where they are diagnosed to have bronchial asthma during their first encounter and others may diagnose them to have laryngotracheobronchitis, acute laryngitis, chronic bronchitis and vocal nodules [7,32,41] and therefore impeding early diagnosis and consequently delaying the act of instituting treatment to such patients. Chest x-ray is usually unreliable, and this is the commonly ordered investigation in children presenting with chronic cough and dyspnea [41]. Such children may go undiagnosed for years especially with the clear chest radiographs.

Treatment Modalities for RRP

Upon establishing the diagnosis of RRP with the aid of indirect laryngoscopy/direct laryngoscopy and sending the biopsy specimen for histology for the first time when such specimen is taken, then strategies towards minimizing number of annual surgeries should be kept in mind. There are several surgical options which have been practicable in various hospital settings in different parts of the world such as micro laryngeal surgery, microdebriders, angiolytic and carbon dioxide laser. None has been proven to be superior compared to the other [12]. Placement of a tracheotomy tube is the oldest treatment modality for RRP disease. Although generally avoided today, it is occasionally still necessary for advanced disease or stenotic complications [42]. Concern has been raised regarding the role of tracheotomy tubes in potentiating distal spread of RRP [26-43].

The carbon dioxide (CO₂) laser has been a mainstay of treatment for RRP since its introduction to endolaryngeal surgery in the 1970s. Laser energy is absorbed by water in the tissues resulting in ablation, and when coupled with an operating microscope, may result in precise, hemostatic vaporization of papillomas with minimal damage to underlying normal tissues [12].

Adjuvant therapies used for RPP include interferon, cidofovir, indole-3-carbinol, ribavirin and acyclovir. As a rare disease there is a serious lack of large population studies to prove the efficacy of these drugs. Up to now, the most extensively investigated adjuvant therapies are interferon-alpha (1990) and cidofovir (2000) [4]. Subcutaneous interferon was first introduced in 1990 but has been recently replaced by cidofovir due to severe associated drug toxicity [44,45]. Cidofovir is a recent antiviral drug, a nucleoside analog, approved by the FDA (Food and Drug Administration) for intravenous use to treat cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. Although it has not been approved for intralesional

administration, cidofovir has been used to treat RPP since 1998, with promising results [4].

Intralesional cidofovir should be started when surgical debulking is required every 2-3 months. Administration should remain below to the established safety limits of dosing (3 mg/kg) and volume [28,46-51]. Its safety profile has recently been debated because of a possible eventual oncogenic potential but that risk has not been confirmed by recent human studies and it has been recommended for the treatment of moderate to severe RPP [52]. However, high quality data are needed and so informed consent (including discussion of off-label use and acute kidney injury, especially in children), is mandatory. Despite the multiple therapeutic protocols used by physicians, no consistently effective treatment of RRP is available to date. Immunotherapy has also been suggested by other studies as one of the treatment modalities for RRP and it involve administration of Heat shock protein E7 which is the fusion protein of recombinant heat shock protein 65 from *Mycobacterium bovis* and the E7 protein from HPV-16. Subcutaneous administration of three doses of heat shock protein E7 after debulking surgery showed significant lengthening of surgical intervals, especially in female patients. This product is not currently commercially available but may have some clinical use in the future.

Possibility of Malignant Transformation of RRP

Most cases of documented RRP are cytologically benign and rarely undergo malignant transformation; however, squamous cell carcinoma (SCC) can arise from RRP in the absence of identifiable risk factors such as radiation, extraesophageal reflux and smoking and this applies to those with Adult Onset RPPs where such individuals may have exposure to carcinogens during one's life where he/she may be suffering from RPPs too.

Malignant transformation in RRP has been reported but no consensus has been established to date as to what may predispose an individual to with laryngeal papillomatosis to end up with cancer of the larynx. Some studies have analyses molecular component of such individual and concluded the synergistic presence of HPV-11 infection and a mutated p53 tumor suppressor gene might be involved in malignant progression of the RRP [8]. Another study reported malignant transformation of RRP to epidermoid carcinoma and this was observed with HPV-11 and this lies in line with what has been reported in literatures where the HPV-11 subtype is associated with a risk of malignant transformation though it's a low risk subtype [4].

Conclusion

RRP is relatively a benign disease and has been a subject of concern in clinical practice due to its potential morbidity and mortality both in children and adults. HPV subtypes 6 and 11 were found to be the etiological agents with subtype-11 associated with a risk of malignant transformation among the

two subtypes. Natural history of RRP has remain to be quite variable and include spontaneous regression, persistence, and dissemination of lesions causing airway compromise and, in rare instances, undergoing malignant transformation to squamous cell carcinoma. Clinicians should have a high index of suspicion when encountering patients with chronic cough, dyspnea and hoarseness of voice since they may be misdiagnosed thus ending up with upper airway obstruction which is potentially fatal. Efforts should be directed towards innovation of curative treatment since no effective curative treatment modality is available to date and thus surgery has remained to be the main stay of treatment. Conclusively, knowledge of etiology, clinical features, treatment modalities of the disease is essential to suggest a correct diagnosis, which must be confirmed by histopathology.

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