

Recurrent Respiratory Papillomatosis: an extensive review

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Abstract

Recurrent respiratory papillomatosis (RRP) is characterized by the recurrence of benign tumors (papillomata) in the aero digestive tract caused by Human Papilloma Virus. The burden for the patient and the society is non negligible, due to the high frequency of repetitive surgeries. The disease follows a bimodal age distribution. Usually the very first manifestation is hoarseness or voice changes but if neglected it can cause airway obstruction resulting in respiratory stridor or acute respiratory distress. The treatment is challenging, includes surgery (mostly CO2 laser) and adjuvant medical therapy is almost always required (Cidofovir, interferon α , and others). The risk of malignant transformation is not negligent. Advances in immunology will lead us to understand the biology of HPV and will permit successful therapies. Prophylactic HPV vaccines are a promising area of research concerning RRP.

Key words: Human Papilloma Virus, Laryngeal, CO2 laser, Cidofovir, treatment

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Epidemiology

Recurrent Respiratory Papillomatosis is a rather rare disease of the aero digestive tract, caused by the Human Papilloma Virus (HPV) and almost exclusively by the subtypes HPV 6 and HPV 11 (the others subtypes causing less than 2% of laryngeal papillomas (1, 2). Sir Morrell Mackenzie (1837–1892) was the first to recognize papillomas as a lesion of the laryngopharyngeal system in children in the late 1800s. It is now apparent that these benign tumors may occur at other parts of the upper gastrointestinal and respiratory tracts, and in all age groups. According to Lindeberg, the disease follows a bimodal age distribution. The first pick is observed in patients younger than 5 years old (juvenile onset recurrent respiratory papillomatosis) and the second in patients during the 3rd decade of their life (adult onset recurrent respiratory papillomatosis) (3) although these limits are not strict. The mode of contamination in the pediatric population remains arguable. The majority of pediatric population gets infected by vertical transmission during delivery by mothers presenting active or latent HPV infection. An uncomplicated vaginal delivery in a mother

with HPV infection has been estimated to carry a risk of transmission of 1:80–1:1,500 (median of 1:400) (4). In utero contamination is also possible. Armbruster-Moraes E et al, proved the presence of HPV in the amniotic fluid in 65% of pregnant women with clinical cervical HPV lesions (5). Sexual transmission generally has not been considered as a possible etiology of JORRP although we have to keep in mind cases of sexual abuse especially in children more than 5 years old. In the adult population the contamination requires a genital skin or oral mucosa contact, including oral to genital contact. The complete sexual maturity occurs in the 3rd decade of life which explains the second pick. Data suggest that horizontal transmission of HPV from patients with RRP to their siblings or other family members is highly unlikely, as the virus was not detected (other than in the papilloma itself) in the upper aerodigestive tract of patients and caregivers (102). The incidence is estimated at 3.4 per 100,000 in children and 1.8 per 100,000 in adults (4). Lori R. Armstrong et al. demonstrated that the age of diagnosis and years of disease did not differ significantly between boys and girls in JORRP (6). In JORRP, according to Bishai et al, the average

duration of illness is 4.2 years during which each patient undergoes 4.4 surgical procedures per year; a ratio of follow-up office visits to surgery is 3 to 1; and the tracheotomy rate is 11%. Juvenile-onset RRP may persist for many years, resulting in physical and emotional sequelae. The annual cost for a single case of JORRP is \$57,996 (range, \$32,407-\$94,114). The annual cost of JORRP in the United States is between \$40 million and \$123 million depending on the prevalence (7). The disease may be benign but the treatment is long, expensive and exhausting for the patients and their families.

Pathogenesis

HPVs are members of the family Papillomaviridae which counts 200 different subtypes, divided into high-risk and low risk according to their carcinogenic potential (8a). It is now well known that the subtypes HPV6 and HPV 11, considered to belong into the low-risk group, are responsible for RRP and genital warts, whereas the HPV 16 and HPV 18 are usually found in cervix, vulvar, penile, and anal dysplasia (8b,9). They are small non-enveloped viruses, with a double stranded circular DNA genome encapsulated within icosahedra capsid composed of 72 capsomeres that replicate within the nuclei of infected host cells. In laryngeal papillomatosis viral DNA is in episomal form in the nuclei of the host cell, contrarily in high-grade intraepithelial neoplasia and cancers in which HPV DNA is generally integrated into the host genome.(10). The viral DNA codes for 8 genes, six early proteins (E1, E2, E4, E5, E6 and E7) all involved in viral replication and oncogenesis, two late proteins (L1 and L2) which are structural proteins for the viral capsid, and a non-coding regulatory region, namely long-control region (LCR) (11,12). This region also contains the highest degree of variation in the viral genome. The mutagen role of HPV is complex. First of all, the HPV E6 gene protein binds to tumor suppressor protein p53 and targets it for rapid degradation (13). As a consequence, the normal activities of p53 which govern G1 arrest, apoptosis, and DNA repair are inhibited. On the other hand, E7 protein binds to the retinoblastoma tumor suppressor gene. The E7 gene product can also

associate with other mitotically interactive cellular proteins such as cyclin E (14). This results in a normal basal cell proliferation, but the terminal differentiation is abnormal and leads to the hyperplasia of the papillomas (15, 16, 17).

The papillomavirus interferes with the immune system of the host, which makes it difficult to treat. First of all; the virus seems to be latent in the respiratory tract of many patients who present laryngeal pathology other than papillomatosis (18). One mechanism used by HPV to evade immune detection by HPV-specific cytotoxic T cells (CTC) is to down-regulate MHC-I (major histocompatibility complex) expression on HPV-infected cells. Simultaneously there is a concomitant down regulation of the antigen presentation protein (TAP-1). Vambudas et al demonstrated that the patients who tend to have a rapid recurrence of the disease, had significant reduction of TAP-1 expression (19). DeVoti proved that RRP is a disease characterized by a local defective TH1-like response in adaptive immunity (20)

Histology

The typical lesions resulting from HPV infection are abnormal squamous maturation with parakeratosis, retardation of superficial cell maturation, papillomatosis, and basal hyperplasia (21). HPV induces an increase of EGFR (epithelial growth factor receptor) in the infested cells. The stimulation from the EGF doesn't result in proliferation of the papillomas. On the contrary a decrease of differentiation of the cells occurs (24, 25). Finally, Rahbar A. et al suggested that the expression of VEGF (vascular epithelial growth factor) and his receptors (VEGFR-1 and VEGFR-2) is increased in the epithelium of squamous papillomas (26). The lesions can be diffused or multifocal. The papilloma lesions seem to have an affinity for anatomic sites where ciliated and squamous epithelia are juxtaposed. The classical sites for recurrent disease in the upper aero-digestive tract would be the nasopharyngeal area of the soft palate, limen vestibuli, mid zone of laryngeal area of the epiglottis, upper and lower margins of the ventricle, vocal fold undersurface, carina and bronchial spurs(22)

Symptoms

JORRP is most commonly diagnosed in children between 2 and 3 years of age and the very first manifestation is hoarseness or voice changes. Less commonly the first manifestation can be an airway obstruction by papillomas resulting in respiratory stridor or acute respiratory distress. In AORRP the diagnosis is made in the 3rd decade of life and the symptoms are quite similar. The diagnosis may be delayed, due to the fact that the disease is rare and it seems like common laryngeal pathologies such as nodules of the vocal cords or laryngitis. If it is ignored, acute respiratory distress and respiratory stridor occurs. Other symptoms are chronic cough, paroxysms of choking, recurrent respiratory infections, or failure to thrive. It is strongly suggested that if patients and mostly children don't respond to the usual therapy, they must be referred to an ENT department. In the majority of cases, the papillomas are confined to the larynx, but we have to keep in mind that 5% of patients' exhibit more distal involvement of the trachea and involvement of lung parenchyma occurs in less than 1% of cases (27, 28, 90-92).

HPV 11 is identified in the majority of cases. Pulmonary papilloma lesions begin as asymptomatic, noncalcified, peripheral nodules but soon enlarge and undergo central cavitation, liquefaction, and necrosis.

Diagnosis

The first examination usually is an indirect laryngoscopy which reveals warts-like masses obstructing the larynx. Like grape clusters, the lesions are translucent, pale pink or sometimes whitish in color. A direct laryngoscopy is then performed in the operating room under general anesthesia and a biopsy is taken. Diagnosis of HPV is made using polymerase chain reaction (PCR), dot blot hybridation, immunohistochemistry and in situ hybridation (29). Detection of HPV mRNA of the E6 and E7 transforming genes is a new method of diagnosis, seems to be 100% sensitive (11). Some studies propose complementary methods for evaluate respiratory papillomatosis (high resolution ultrasound, virtual bronchoscopy, a multimodality bronchoscope comprised of white light bronchoscopy (WLB), endobronchial ultrasound (EBUS), and optical

coherence tomography (OCT) , and also the PET CT scan) but none can replace the laryngoscopy. (30-32).The physician must have in mind that laryngeal papillomatosis can invade the local structures. A complete examination includes a full panendoscopy to exclude migration into the pharynx, trachea and esophagus.

Staging

Derkay et al proposed a staging system to increase the reliability between surgeons. They divided the aerodigestif tract into 25 areas. Each one was given a score, from 0 (no lesion) to 3 (bulky lesion) (33, 34). This staging system has proven to be quite reliable (35), but not used in the common practice.

Risk factors

The virus is thought to gain entry to its host cell, the basal keratinocyte, by microtraumas or abrasions to the surface epithelium. Mothers with active or latent condylomas can transmit the virus to their newborns during vaginal delivery. The risk has been estimated to 7 children with laryngeal papillomatosis for every 1000 women with a history of genital warts (28). Mounts et al, demonstrate that a maternal history of genital warts in pregnancy was identified as the principal risk factor for the development of JORRP. They identified longer delivery times (at least 10 hours) and not living with the newborn's father as additional cofactors (36). In these cases a cesarean section should be considered, even if there is suspicion of transmission via the blood or the amniotic liquid (5, 37). In AORRP the main risk factor is the sexual oro-genital contact with a person who has active or latent condylomas.

Treatments

Many treatment modalities for RRP have been tried, some of them more efficacious than others, but none of them has been proven fully efficacious for a cure in all patients.

Surgical

Suspension microlaryngoscopy with CO2 laser is still the treatment of choice. It replaced the conventional surgery with scalpel successfully at the early 1970's, providing microscopic precision, decreases the change of infection, offers a bloodless operative field and complete

sterility and reduces healing time and swelling, (39-43). Patients have to undertake several operations in order to control the disease. Airway fire, airway perforation, anterior glottic webbing, interarytenoid scarring and arytenoid fixation, vocal cord fibrosis, and generalized endolaryngeal glottic stenosis are some complications of the thermal energy generated by this

Instrument (44), but is still the gold standard in the hands of a well trained surgeon.

The surgeon has to be very careful to protect the surrounding tissues from thermal lesions (eyes and skin). The patient, the surgeon, and the operating room staff may inhale the surgical plume, which may contain the human papillomavirus DNA, as demonstrated by Kashima et al (45). Special precautions must be taken from the medical staff in the operating room. Regarding the anesthesia management, the usual techniques are the endotracheal intubation or jet ventilation.

Laser surgery by fiber-guided Nd: YAG (neodymium yttrium aluminum garnet) laser is known since the late 80's but mostly used in other pathologies. It is very effective for coagulation, due to the fact that it is absorbed mostly by hemoglobin. It is weakly absorbed by water so has the advantages of a greater penetration depth in tissues. Another advantage is that it can be delivered through a fiberoptic carrier. Some cases were reported having been treated successfully but the sample is too small for making conclusions (46-49). The 532 manometer pulsed potassium-titanyl-phosphate laser (KTP laser) is a frequency-doubled Nd: YAG laser. It is used already in benign pathology of the larynx. The green light produced is absorbed chiefly by the hemoglobin in the microvascularisation which allows a precise excision of the lesion without thermal damage. Its beam can be delivered through flexible fibers. Burns et al presented promising results but further investigation is required (50, 51).

An alternative to the CO₂ laser is the 585 manometre pulsed-dye laser. The radiation is transmitted through a standard silica optical fiber which offers an easy use. Contrary to the CO₂ laser, it is absorbed by oxyhemoglobin in erythrocytes, so thermal damage is confined to the walls of microvessels and nearby

perivascular space. It is mainly used for telangiectasies, livid port-wine stains and hemangiomas. Some studies suggested that pulsed dye laser is an effective alternative causing less collateral damage but more studies must be made (52, 53). When papillomata are present in the tracheobronchial tree, it is often necessary to use KTP or pulse dye laser coupled with a ventilating bronchoscope.

Argon laser, radiofrequency cold ablation and microdebrider are also mentioned in the literature for treating RRP but further investigation is required devices used for RRP a type of ion laser which use a noble gaz. It is absorbed by hemoglobin and melanin. It undergoes little absorption and transmission so it is mostly used for vascular and pigmented lesions. Some case reports shown promising results. (54)

Radiofrequency cold ablation (coblation) is commonly used in other pathologies but during the last 5 years studies suggested that it is an attractive alternative, although further investigation should take place (55-58)

Medical

The current criteria for adjuvant therapy are the necessity for more than 4 surgical procedures annually, rapid regrowth of papillomata with airway compromise and/or remote multisite spread of the disease (59).

Cidofovir [(S)-1-(3-hydroxy-2-phosphonyl methoxypropyl) cytosine] is the gold standard in the adjuvant therapy in RRP. Is a cytosine nucleotide analogue with antiviral activity that is approved by the US Food and Drug Administration (FDA) for the treatment of cytomegalovirus (CMV)-retinitis in persons with acquired immunodeficiency syndrome. The long intracellular half-life of cidofovir and its metabolites allows for infrequent dosing. Usually studies report two different ways of using it: intravenous and intralesional. About intralesional use of Cidofovir which is more used, the studies are inconclusive about the efficiency. Many studies demonstrate that intralesional Cidofovir improves all patient outcomes (60-66). Cochrane Database Systematic Review suggests that there is no significant difference comparing to a placebo but in the review only one randomized control trial met the inclusion criteria, so the power is

limited (67). The main difficulty in evaluating the efficiency is that there is no protocol established for the doses or the number of injections. There were some concerns about the carcinogenic properties of this particle. Some published articles mentioned an increase of malignant transformation (68). A review of the literature showed that the percentage of degeneration after intralesional Cidofovir, is 2.7% of the patients (69) which is the incidence of the spontaneous malignant degeneration of HPV (all subtypes included) (2–5%)(70,71). Some studies reported nephrotoxicity, neutropenia and partial alopecia. To minimize the side effects the dose of intralesional Cidofovir must not exceed 3mg/kg, and the injection can be repeated over the time. The use in pregnancy is prohibited. Intravenous use of Cidofovir is reserved for very aggressive forms with pulmonary involvement with good results (72-76)

The interferons are a group of cytokines produced by leucocytes in response to viral, bacterial and tumoral stimulation (77). The most studied cytokine for viral infection and one of the most effective ones is INF- α . The administration mode can be intravenous, intramuscular or subcutaneous. Two large studies observed a very good therapeutic response if the patient had been infected by HPV 6, and not that good when infected by HPV 11 (78, 79). How many weeks and when do we consider the treatment effective? Side effects that could be observed are fever, drowsiness, increased bronchial secretion, chills and headache.

Mytomycin C is an antineoplastic antibiotic produced by *Streptomyces caespitosus*. It is one of the bi- or tri-functional alkylating agents causing cross-linking of DNA and inhibition of DNA synthesis. A limited sample study suggests that the local administration of mitomycin C (1 cc of 0.5 mg/ml) as an adjuvant therapy to laser surgery is an alternative to the treatment of RRP. (80)

Photodynamic therapies (PDT) Shikowitz et al used meso-tetra (hydroxyphenyl) chlorine as a photosensitizer and compare it with the classical approach of CO₂ laser. The study reveals a slow necrotic destruction of papilloma tissue, with modifications of the immune system of the host, but the response was not

permanent. Studies were not conclusive about the advantages and efficacy comparing to CO₂ laser (81).

Cis retinoid acid, ribavirine, indole-3-carbinol and acyclovir are some of the drugs tested for the effectiveness on laryngeal papilloma but they provide a wick argument concerning their efficiency (82-87).

Antireflux therapy has been studied as a complementary treatment. Cimetidine is an H₂-receptor antagonist. According to studies, there are two theories about the benefit of adding the drug to the treatment plan. The first one claims that cimetidine in high doses is an immunomodulator with inhibitory effects on suppressor-cell function. (87, 88). Patients with RRP, after treatment with antireflux therapy, showed some improvement. The second one claim, according to Mckenna et al, that the clinical expression of papillomatosis could be triggered by the inflammation due to the chronic exposure of reflux, based on the fact that HPV stays latent in the respiratory tract (89). Although is an attractive theory research needs to be done.

Gardasil The recently developed tetravalent HPV vaccine Gardasil induces neutralizing antibodies against capsid antigens. It has been shown that the expression of papilloma virus L1 genes in vitro, induces high titers of virus-neutralizing serum antibodies when administered as an immunogen. There are some case reports describing a stabilization of the disease in the very aggressive forms, which is promising but further studies must be done (103,104)

Prognosis

The course of recurrent respiratory papillomatosis is variable. Some patients need one or two surgical procedures with variable remission period between them, for others is a chronic, frequently debilitating, and potentially life-threatening disease demanding repetitive surgeries. Factors affecting the time course of RRP include: inter-surgeon variability, the extent and severity of papillomas at the time of laryngoscopy, the use of adjuvant medical therapies and the subtype of HPV. Clinically, papillomatosis with HPV 11 has a more aggressive course comparing to HPV 6 (90, 91). According to Blumin and al (92), 21% of

the patients with AORRP present at one point of the disease with dysplasia, which is approximately the same for JORRP (7). An important prognostic factor of RRP is the presence of trachea or lung invasion. According to a review of the literature it is estimated around 3, 3 % in JORRP (90) and it is associated with an aggressive form of the disease. According to the same study 16% of patients with lung involvement will develop lung squamous cell carcinoma. When the upper airway is compromised and the papillomas obstruct the larynx, tracheotomy is part of the treatment management. With time, there were some concerns. Some studies suggested that the injury associated with tracheotomy may contribute to the distal spread of the disease (101). The disease has a predilection for squamo - columnar junctions and tracheotomy creates just such a junction. We have to keep in mind, those patients who requires tracheotomy, have already an aggressive form of the disease and the distal spread could be inevitable. Follow up is crucial. Dedo and al, in a large cohorte of 244 patients, suggested a close follow up every 2 months and additional surgery if needed (43). Patients younger than 3 years of age at RRP diagnosis are prone to develop more aggressive disease as represented by higher severity scores at endoscopic debridement, more frequent operative debridement procedures per year, a greater requirement for adjuvant therapy, and greater likelihood of tracheal disease with tracheotomy y (93, 94). On the other hand, sex and race don't seem to affect the course of the disease. Studies suggest that the status of immunocompetancy of patients is critical. Patients who develop RRP manifest a tolerance against HPV infection as a result of inappropriate and inadequate immune response (95-99).

Conclusion

Recurrent respiratory papillomatosis continues to be a highly morbid disease process. Despite new surgical and medical therapies in some cases, treatment fails. During the last decade, advances in immunology led us to understand the working mechanism of HPV and its complex interaction with the host. Further research is needed in how to induce immune system modulation of the host.

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