REVIEW

Recurrent respiratory papillomatosis

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Recurrent respiratory papillomatosis (RRP) is a benign, often multi-focal neoplasm.[1] A potentially fatal manifestation of human papilloma virus infection, the condition is characterised by multiple warty excrescences on the mucosal surface of the respiratory tract. RRP is rare—incidence is estimated at 3.5 per million person-years,[2] with a prevalence of 4 in 100 000 children. Affected children usually require multiple interventions; the impact on patients, their families, and the healthcare system is considerable. Treatment of RRP accounts for an estimated $109 million annual expenditure in the USA.[2]

RRP is caused by the human papilloma virus (HPV). HPV types 6 and 11 are the most common aetiological agents, with HPV-11 conferring a most aggressive course.[3] HPV types 6 and 11 are also associated with maternal genital warts. The virus is thought to be transmitted at birth by contact with infected secretions in the birth canal. The traditionally quoted susceptibility factors for RRP are first-born children, maternal genital warts, young maternal age, vaginal delivery, and low maternal socioeconomic status,[2 4] but often none of these is applicable. In the case of children born to mothers with genital warts, HPV DNA has been found in one third to one half of aerodigestive tract swabs of children born to these mothers, but very few of these children—1 in 400—develop RRP.[5 6] HPV is common in the maternal genital tract (up to 25%), but RRP is rare, suggesting that host susceptibility plays an important part in aetiology. Caesarean section was at one time recommended—particularly in the USA—for mothers with genital warts but current evidence does not support this.[7]

Despite recent work on HLA polymorphisms which may help to identify pregnancies where the infant is at particular risk, host susceptibility is currently unpredictable.

PRESENTATION AND DIAGNOSIS

The larynx is the most commonly affected site. Presentation is classically with progressive hoarseness—typically at age 3 or 4 years. Age at diagnosis is the most important predictor of disease severity—patients presenting before 3 years old have more multicentric disease, require more frequent surgery, and more often need tracheotomy.[8]

A delay in diagnosis of RRP is not uncommon. Symptoms can be variable and mimic common laryngeal and respiratory pathologies in children, e.g. vocal cord nodules, laryngitis, asthma, bronchitis, or croup. Paediatricians and primary care physicians sometimes make a clinical diagnosis of vocal cord nodules, but despite the rarity of RRP we would urge caution and suggest that any child who presents with hoarseness which does not quickly respond to treatment, should be referred to ENT for endoscopy of the larynx. This is now a straightforward procedure which most children tolerate under local anaesthesia in the outpatient department. Failure of diagnosis or an uncooperative child, with a high index of suspicion, results in the decision to proceed to assessment under general anaesthesia.

Younger children may present with an abnormal cry or with airway obstruction. In addition to hoarseness and stridor, there may be a chronic cough, paroxysms of choking, recurrent respiratory infections, or failure to thrive.

The diagnosis is confirmed endoscopically under general anaesthesia where the warty appearance of the excrescences is seen, most often on the larynx but in severe cases in the tracheobronchial tree.

Final confirmation is histological. Viral subtyping is increasingly requested to help predict prognosis.

COURSE

Although histologically benign, epithelial proliferations may result in progressive hoarseness, stridor, airway obstruction, and respiratory distress. RRP is a serious and potentially life threatening disease. Surgical debulking may need to be frequent in the early stages to maintain a patent airway. The clinical course is unpredictable, some children requiring no more than six monthly surveillance, and some needing frequent admissions for rapidly progressive lesions. Periods of quiescence may be followed by episodes of rapid proliferation and vice versa. Severely affected children may develop tracheal, or even worse, tracheobronchial spread.

Advanced disease may be complicated by pulmonary cavitation. Fatal transformation to squamous cell malignancy in adolescence or early adult life has been reported, particularly with HPV-11.[9] Traditional teaching is that the disease goes into remission in adolescence but severe cases persist into adult life. Early spontaneous remission of RRP has been reported.

SURGICAL TREATMENT

Management is directed at maintaining a safe airway and a good voice by repeated surgical debulking. Children require a mean of 4.1–4.4 procedures during their first year after diagnosis.[10] Surgery is carried out endoscopically with endolaryngeal instruments, laser (principally the

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carbon dioxide laser), or increasingly, the ''microdebrider''—a suction device introduced endoscopically under direct vision, that engages the affected tissue, which is then fragmented by a rapidly rotating integral blade. The microdebrider is fast becoming the first choice surgical modality in many centres due to its ease of use and its lack of damage to tissues surrounding the excrescences.

Tracheotomy—a last resort

Much of the concern about the deleterious influence of tracheotomy on the course of the disease may relate to the fact that children who require tracheotomy are inevitably those with aggressive disease to start with. Nevertheless tracheotomy is avoided if at all possible. The disease has a predilection for squamo-columnar junctions and tracheotomy creates just such a junction. Papillomas rapidly colonise the tracheotomy site and distal spread becomes more likely. Tracheotomy may be the prelude to extensive proliferative tracheobronchial disease which can be fatal.

In aggressive disease however, where there has been a poor response to repeated surgery, adjuvant therapy tracheotomy may be the only safe way to manage the child's airway.

MEDICAL TREATMENT

RRP is a viral condition. It is logical to think that treatment should be medical. Given the propensity for bulky lesions to obstruct the airway, surgery remains the primary treatment with medical interventions reserved as adjuvant therapies.

Interferon

One of the earliest adjuvant treatments was interferon. Interferons—now manufactured commercially by recombinant DNA technology—are proteins naturally produced by human leucocytes in response to a variety of stimuli, including viral infection.

Interferon binds to specific membrane receptors and alters cell metabolism, having antiviral, antiproliferative, and immunomodulatory effects. The exact mechanism of action on laryngeal papillomatosis is not known. In an early multicentre controlled study, 123 patients were randomly assigned to receive surgery alone or surgery plus interferon, and observed for two years. Intravenous interferon alpha (IFNα) was given daily for one week followed by three times per week for one year. Follow up was for a further year. A significant decrease in disease progression in the IFNα group was noted in the first six months but this was not sustained. It was concluded that interferon is neither curative alone nor of value as an adjunctive agent in the long term.[11]

Clearly the evidence relating to interferon is equivocal. There are anecdotal reports and data from uncontrolled studies of dramatic response in some children.[12 13] The principle limitation is toxicity, including transient fever, fatigue, nausea, arthralgia, and headache. There may be reversible increases in serum transaminase levels. More seriously, leucopenia and thrombocytopenia have been reported, as has spastic diplegia in infants.

The data presented relate to systemic (intravenous) administration of interferon. There are anecdotal reports of it being injected intralesionally at the time of surgery.

Intralesional cidofovir

The antiviral agent cidofovir—a cytosine analogue—is active against a broad spectrum of DNA viruses. The precise mechanisms of action against HPV are not well understood, but induction of apoptosis and augmentation of immune responses have been proposed.[14] Injection of cidofovir to the base of the lesions at the time of surgery has been reported since the early 1990s.

In prospective studies, adjuvant intralesional cidofovir has resulted in partial to complete regression of papillomas and decreased need for surgery.[15–21] It appears that intralesional administration does not produce systemic toxicity or local side effects. The cidofovir plasma levels are below those leading to toxicity and are dose dependent in children.[21] Long term risks associated with administration of intralesional cidofovir are uncertain but there is the theoretical risk of malignant transformation. There is no accepted protocol for dose, frequency of administration, or drug concentration.[22]

Systemic cidofovir has also been tried but reports are few and anecdotal.[23]

Other antivirals

Ribavirin is a broad spectrum antiviral which has been used both as an aerosol and systemically. Evidence is anecdotal and it is not widely used.[24] Acyclovir is not directly active against HPV but it has been used. Evidence of efficacy is weak.[25]

Indole-3-carbinol

Indole-3-carbinol (I3C) is derived from cruciferous vegetables (sprouts, broccoli, cabbage) and is known to affect papilloma growth in vitro through its effect on oestrogen metabolism. Evidence of clinical efficacy is again equivocal. In a prospective study, nine children were treated with adjuvant I3C orally. At follow up (4.8 years), there was one ''complete responder'' and three ''partial responders''. No adverse effects were noted.[26]

Mumps vaccine

Mumps vaccine has been used intralesionally as an adjuvant. In an uncontrolled study of 29 children, injections were given at the time of surgical laser excision every 3–12 weeks. Children were regarded as ''in remission'' after at least one year follow up and two consecutive negative endoscopies. Twenty three children remain ''in remission'' (i.e. disease free for one year and with two negative endoscopies) after 2–19 years follow up. The mechanisms are unclear but the authors feel that intralesional adjuvant mumps vaccine influences induction of remission in children RRP with a low risk of adverse side effects.[27]

HspE7

This is a recombinant fusion protein of Hsp65 of *M bovis* BCG and E7 protein from HPV 16. In an open label study, 27 patients were given 500 μg HspE7 subcutaneously, monthly for three doses over three months, and followed for up to five years. There was a statistically significant decrease in the patient's annualised frequency of surgery and in the absolute number of surgical procedures needed with only mild to moderate local injection reactions.[28]

Control of gastro-oesophageal reflux disease

The presence of laryngopharyngeal reflux disease has been associated with worsening manifestations of RRP and increased treatment complications. Studies have shown that treatment with cimetidine or a proton pump inhibitor has resulted in improved control of RRP and even complete remission.[29 30]

CONCLUSION

As the pathophysiology of HPV disease unravels, there remains the intriguing possibility of a vaccine. A quadravalent HPV vaccine targeting types 6, 11, 16, and 18 could substantially reduce the acquisition of infection and clinical genital disease caused by common HPV types.[31]

No known single or combination treatment reliable eradicates HPV. Because of its low incidence and erratic behaviour there is a need for further well designed multicentre, multidisciplinary, and international trials to generate

data with sufficient power to clarify the role of adjuvant medical therapy.

The aim of a cure with the least morbidity should guide our further search.

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REFERENCES

1 **Morgan AH**, Zitch RP. Recurrent respiratory papillomatosis in children: a retrospective study of management and complications. *Ear Nose Throat J* 1986;**65**:19–28.
2 **Derkay CS**. Task force on recurrent respiratory papillomas: a preliminary report. *Arch Otolaryngol Head Neck Surg* 1995;**121**:1386–91.
3 **Rabah R**, Lancaster WD, Thomas R, *et al*. Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease. *Pediatr Dev Pathol* 2001;**4**:68–72.
4 **Kashima HK**, Shah F, Lyles A, *et al*. A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis. *Laryngoscope* 1992;**102**:9–13.
5 **Shah K**, Kashima HK, Polk BF, *et al*. Rarity of caesarean delivery in cases of juvenile-onset respiratory papillomatosis. *Obstet Gynecol* 1986;**68**:795–9.
6 **Tenti P**, Zappatore R, Migliora P, *et al*. Perinatal transmission of human papillomavirus from gravidas with latent infection. *Obstet Gynecol* 1999;**93**:475–9.
7 **Kosko JR**, Derkay CS. Role of cesarean section in prevention of recurrent respiratory papillomatosis—is there one? *Int J Pediatr Otorhinolaryngol* 1996;**35**:31–8.
8 **Wiatrak BJ**, Wiatrak DW, Broker TR, *et al*. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. *Laryngoscope* 2004;**114**(11, pt 2, suppl 104):1–23.
9 **Reidy PM**, Dedo HH, Rabah R, *et al*. Integration of human papillomavirus type 11 in recurrent respiratory papilloma-associated cancer. *Laryngoscope* 2004;**114**:1906–9.
10 **Armstrong LR**, Derkay CS, Reeves WC. Initial results from the National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis. *Arch Otolaryngol Head Neck Surg* 1999;**125**:743–8.
11 **Healy GB**, Gelber RD, Trowbridge AL, *et al*. Treatment of recurrent respiratory papillomatosis with human leukocyte interferon. Results of a multicenter randomized clinical study. *N Engl J Med* 1988;**319**:401–7.
12 **Leventhal BG**, Kashima HK, Weck PW, *et al*. Randomized surgical adjuvant trial of interferon alfa-n1 in recurrent papillomatosis. *Arch Otolaryngol Head Neck Surg* 1988;**114**:1163–9.
13 **Nodarse-Cuni H**, Iznaga-Marin N, Viera-Alvarez D, *et al*. Interferon alpha-2b as adjuvant treatment of recurrent respiratory papillomatosis in Cuba: National Programme (1994–1999 report). *J Laryngol Otol* 2004;**118**:681–7.
14 **Shehab N**, Sweet B, Hogikyan ND, *et al*. Cidofovir for the treatment of recurrent respiratory papillomatosis: a review of the literature. *Pharmacotherapy* 2005;**25**:977–89.
15 **Pransky SM**, Albright JT, Magit AE. Long term follow up of paediatric recurrent respiratory papillomatosis managed with intralesional cidofovir. *Laryngoscope* 2003;**113**:1583–7.
16 **Milczuk HA**. Intralesional cidofovir for the treatment of juvenile recurrent respiratory papillomatosis: long term follow up of 4 children. *Otolaryngol Head Neck Surg* 2003;**128**:788–94.
17 **Akst LM**, Lee W, Discolo C, *et al*. Stepped-dose protocol of cidofovir therapy in recurrent respiratory papillomatosis in children. *Arch Otolaryngol Head Neck Surg* 2003;**129**:841–6.
18 **Lee AS**, Rosen CA. Efficacy of cidofovir injection for the treatment of recurrent respiratory papillomatosis. *J Voice* 2004;**18**:551–6.
19 **Shirley WP**, Wiatrak B. Is cidofovir a useful adjunctive therapy for recurrent respiratory papillomatosis in children? *Int J Pediatr Otolarhinolaryngol* 2004;**68**:413–18.
20 **Mandell DL**, Armjand EM, Kay DJ, *et al*. Intralesional cidofovir for pediatric respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg* 2004;**130**:1319–23.
21 **Naiman AN**, Ceruse P, Coulombeau B, *et al*. Intralesional cidofovir and surgical excision for laryngeal papillomatosis. *Laryngoscope* 2003;**113**:2174–81.
22 **Derkay CS**. Cidofovir for recurrent respiratory papillomatosis(RRP): a re-assessment of risks. *Int J Pediatr Otorhinolaryngol* 2005;**69**:1465–67.
23 **de Bilderling G**, Bodart E, Lawson BE, *et al*. Successful use of intralesional and intravenous cidofovir in association with indole-3-carbinol in an 8-year-old girl with pulmonary papillomatosis. *J Med Virol* 2005;**75**:332–5.
24 **Morrison GA**, Kotecha B, Evans JN, *et al*. Ribavarin treatment for juvenile respiratory papillomatosis. *J Laryngol Otol* 1993;**107**:423–6.
25 **Endres DR**, Bauman NM, Burke D, *et al*. Acyclovir in the treatment of recurrent respiratory papillomatosis. A pilot study. *Ann Otol Rhinol Laryngol* 1994;**103**(4 pt 1):301–5.
26 **Rosen CA**, Bryson PC. Indole-3-carbinol for recurrent respiratory papillomatosis: long-term results. *J Voice* 2004;**18**:248–53.
27 **Pashley NR**. Can mumps vaccine induce remission in recurrent respiratory papilloma? *Arch Otolaryngol Head Neck Surg* 2002;**128**:783–6.
28 **Derkay CS**, Smith RJH, McClay J, *et al*. HspE7 treatment of pediatric recurrent respiratory papillomatosis: final results of an open-label trial. *Ann Otol Rhinol Laryngol* 2005;**114**:730–7.
29 **Harcourt JP**, Worley G, Leighton SE, *et al*. Cimetidine treatment for recurrent respiratory papillomatosis. *Int J Pediatr Otorhinolaryngol* 1999;**51**:109–13.
30 **McKenna M**, Brodsky L. Extraesophageal acid reflux and recurrent respiratory papilloma in children. *Int J Pediatr Otorhinolaryngol* 2005;**69**:597–605.
31 **Villa LL**, Costa RL, Petta CA, *et al*. Prophylactic quadravalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;**6**:271–8.