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Infantile recurrent respiratory papillomatosis: review of adjuvant therapies

A Patel and N Orban

ENT Department, Royal London Hospital, Whitechapel Road, Whitechapel, London E1 1FR, UK

Abstract

Background. Recurrent respiratory papillomatosis is a potentially life-threatening condition characterised by the growth of exophytic lesions within the larynx and trachea. The principal aim of management is maintenance of an adequate airway by surgical debulking. Several adjuvant therapies have been used to varying effect to reduce the burden of this disease and increase the interval between debulking procedures. The most severe cases present in children aged under three years, who are therefore most likely to need adjuvant therapies. The current evidence base on adjuvant treatments relating to children who present aged under three years has been reviewed.

Methods. A literature review of articles in Cochrane, PubMed and Embase databases was carried out. Given the rarity of the condition in this age group, all the literature relates to case reports and case series.

Results and conclusion. The following adjuvant therapies have been used in children who presented under three years of age: quadrivalent human papilloma virus vaccine, intralesional cidofovir, pegylated interferon, alpha-interferon, cimetidine and cetuximab.

Case summary

An 11-month-old child presented to the emergency department with inspiratory stridor. He had no other medical conditions or immunodeficiency. He was born at term by normal vaginal delivery. He underwent microlaryngoscopy, which confirmed the presence of laryngeal papillomas involving the vocal folds, epiglottis and false cords (Figure 1). He underwent surgical debulking using a microdebrider and carbon dioxide (CO_2) laser. Initially, he required surgical debulking every four weeks to maintain an adequate airway. The requirement for debridement gradually progressed to becoming necessary every three weeks. Now, six months after his initial presentation, he requires surgical debulking every fortnight. The papillomas have extended to involve his subglottis (Figure 2). Adjuvant treatments have not been used at present. We review the literature to identify the surgical and adjuvant therapies that have been used in this age group.

Introduction

Recurrent respiratory papillomatosis is an uncommon condition characterised by the growth of exophytic lesions within the larynx and trachea. It presents with hoarseness or stridor and carries significant morbidity. Currently, the principal aim of management is maintenance of an adequate airway with surgical debulking. This process is repeated at appropriate intervals whilst awaiting spontaneous resolution of the condition. A number of adjuvant therapies have been used with varying effect to expedite the cessation of papillomas.

Recurrent respiratory papillomatosis is categorised as juvenile-onset or adult-onset.[1] In the paediatric population, the incidence varies between 2 and 4 per 100 000.[2,3] Juvenile-onset recurrent respiratory papillomatosis is more aggressive than the adult-onset form. The most severe cases present in children aged under three years.[4,5] Children under three years are 3.6 times more likely to require at least four debulking procedures per year.[4]

The papillomas are histologically benign. Recurrent respiratory papillomatosis is caused primarily by human papilloma virus (HPV) types 6 and 11.[6] Several studies have supported the theory of vertical transmission from affected mothers.[7,8] Vaginal warts are also caused by HPV types 6 and 11, which supports the hypothesis of vertical transmission from mother to child during childbirth. However, recurrent respiratory papillomatosis has also affected children born by caesarean section, and this raises the possibility of *in utero* transmission.[8,9] Caesarean section does reduce the risk of recurrent respiratory papillomatosis by more than four times.[10]

Most commonly, the exophytic lesions are confined to the larynx, but they can be seeded into the trachea, bronchi and oesophagus. Rarely, recurrent respiratory papillomatosis can be fatal, mostly because of acute airway obstruction, diffuse bronchopulmonary spread or malignant change.[11]

Main Article

Dr A Patel takes responsibility for the integrity of the content of the paper

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Author for correspondence:
Dr Ankit Patel, ENT Department,
Royal London Hospital, London E1 1FR, UK
E-mail: ankitpatel@doctors.org.uk

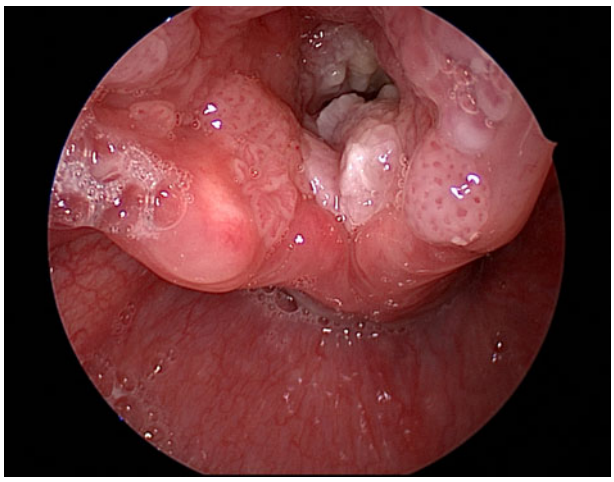

Fig. 1. Evidence of laryngeal and supraglottic papillomas.

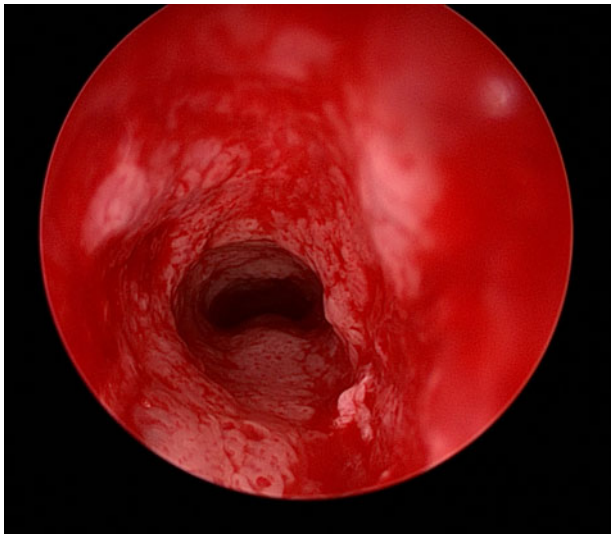

Fig. 2. Evidence of subglottic papillomas.

Adjuvant therapies are traditionally considered when more than four to six debridements are required per year. Several medical adjuvant treatments have been used for recurrent respiratory papillomatosis in both juvenile and adult-onset cases, although none has demonstrated a curative result.[1] Recent systematic reviews are available on adjuvant therapies in paediatric recurrent respiratory papillomatosis.[12–14] Given that the most aggressive recurrent respiratory papillomatosis presents in the youngest children, it is most likely that a child within this age group would need to be considered for adjuvant therapy. Therefore, the current evidence base on adjuvant treatments relating to children who present under three years of age has been reviewed. This appraisal can augment the existing published literature that has already examined adjuvant therapies in wider age groups. Together, they can assist clinicians in applying evidence-based medicine to this complex clinical case.

Methods

A literature review of articles in Cochrane, PubMed and Embase databases was carried out. Abstracts were then studied, and articles that focused on the management of recurrent respiratory papillomatosis in children aged under three years were included. The references of qualifying articles were also searched for relevant papers. We excluded articles if the patient's age at first presentation was unclear or was greater than three years.

Results

The papers that met the inclusion criteria have been summarised in Tables 1 and 2. Given the rarity of the condition in its infantile form, all the literature relates to case reports and case series.

No randomised, controlled trials or systematic reviews have been carried out on this specific age group. For completeness, relevant randomised trials and systematic reviews have been summarised in Table 3, although these do not isolate the results in children aged under three years specifically.

Discussion

Recurrent respiratory papillomatosis presenting under three years of age represents the most aggressive form of the disease.[4] Given the relative rarity of this condition, most literature relates to level 4 and 5 evidence in the form of case reports and small case series. The knowledge base is strongly dependent on larger case series, systematic reviews and a few randomised, controlled trials in the older age groups.

Surgical procedures

All the literature confirms the need for regular surgical debulking of papillomas.[1,15,16] The papilloma bulk is reduced in order to maintain a patent airway and to avoid damaging the underlying tissue. The surgical techniques used include cold steel, CO_2/potassium-titanyl-phosphate (KTP) laser, microdebridement or a combination of these.[16] Some reports have indicated the need for tracheostomy, which is not unusual given the aggression of recurrent respiratory papillomatosis in this age group.[16–18]

The risk of laryngeal scarring (anterior/posterior glottis, supraglottis or trachea) with CO_2 laser in children is well described.[16,19] None of the reviewed articles reported any long-term complications relating to the surgical technique in our intended age group. This is most likely related to the short follow-up periods.

Adjuvant therapies

To reduce the burden of this disease and increase the interval between surgical debulking procedures, several adjuvant therapies have been used to varying effect. These therapies have been used in adults and children. Although there is no specific indication for the use of adjuvant treatment, it is widely considered when the need for surgical debulking is frequent (more than four to six times per year) or if the papillomas begin spreading beyond the larynx. In 21 per cent of juvenile-onset recurrent respiratory papillomatosis cases in the USA, an adjuvant therapy is used in conjunction with repeated debulking surgery.[20] In 2012, Chadha and James published a Cochrane review update on the use of adjuvant therapies for recurrent respiratory papillomatosis in adults and children.[21] They concluded that there was insufficient evidence from controlled trials to support any adjuvant treatment.

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Table 1. Summary of case reports relating to adjuvant treatments used in recurrent respiratory papillomatosis in children aged under three years

Author (year)	Age at presentation	Location of papillomas	Primary treatment	Adjuvant treatment (age commenced)	Follow-up duration*	Outcome
Meszner *et al.* (2014)	3.5 mth	Supraglottis, glottis, oesophagus	3–5 weekly surgical debulking (cold steel or laser)	Quadrivalent HPV vaccine (24 mth)	24 mth	Complete response
Forster *et al.* (2008)	15 mth	Larynx	Unknown	Quadrivalent HPV vaccine	10 mth	Complete response
Katsuta *et al.* (2017)	23 mth	Larynx	3–5 weekly surgical debulking (microdebrider), tracheostomy	Quadrivalent HPV vaccine (27 mth)	3 y	No response
Mudry *et al.* (2010)	2 y	Larynx	3–4 monthly surgical debulking (cold steel or laser)	Quadrivalent HPV vaccine (4 y)	17 mth	Complete response
Harcourt *et al.* (1999)	5 mth	Trachea, bronchi, lung parenchyma	Tracheostomy, monthly surgical debulking (laser)	Systemic cimetidine (10 y)	5 mth	Partial response
Durvasula *et al.* (2013)	6 mth	Larynx	4-weekly surgical debulking (microdebrider or laser)	Intralesional cidofovir (9 mth)	9 mth	Complete response
Loyo *et al.* (2008)	4 mth	Supraglottis, glottis, trachea	Monthly surgical debulking (microdebrider)	Systemic cetuximab (4 mth), intralesional cidofovir (4 mth)	22 mth	No response (cetuximab), partial response (cidofovir)
Ksiazek *et al.* (2010)	4 mth	Supraglottis, glottis, subglottis, trachea, bronchi	2-weekly surgical debulking (microdebrider or laser)	Intralesional cidofovir (6 mth), systemic interferon-alpha (13 mth), nebulised cidofovir (23 mth)	6 mth	No response (intralesional cidofovir), no response (interferon-alpha), complete response (nebulised cidofovir)
Maunsell *et al.* (2017)	14 mth	Larynx, trachea, epiglottis, lung parenchyma	2-weekly surgical debulking (cold steel, laser or microdebrider), tracheostomy	Intralesional cidofovir (17 mth), intralesional bevacizumab (26 mth), PEG-IFN (6 y)	6 mth	No response (cidofovir), no response (bevacizumab), partial response (PEG-IFN)
Bostrom *et al.* (2004)	3 mth	Larynx, trachea, bronchi	Tracheostomy, weekly surgical debulking (laser or cold steel)	Interferon-alpha (3 mth until 8 y), inhaled ribavirin (8–9 y), systemic gefitinib (9 y)	3 mth	Partial response (interferon-alpha), no response (ribavirin), partial response (gefitinib)

*After initiation of adjuvant therapy. Mth = months; HPV = human papilloma virus; y = years; PEG-IFN = pegylated interferon

Table 2. Summary of case series relating to adjuvant treatments used in recurrent respiratory papillomatosis in children aged under three years

Author (year)	Children aged <3 years at presentation (*n*)	Adjuvant therapy	Follow-up duration*	Outcome
Bielecki *et al.* (2009)	3	Intralesional cidofovir	6 mth	Complete response = 1, good response = 1, partial response = 1
Chung *et al.* (2006)	2	Intralesional cidofovir	31–34 mth	Complete response = 1, partial response = 1
Peyton-Shirley *et al.* (2004)	11	Intralesional cidofovir	Unknown	Good response = 3, partial response = 2, no response = 6
Pransky *et al.* (2000)	3	Intralesional cidofovir	9 mth	Complete response = 1, good response = 2
Milczuk *et al.* (2003)	4	Intralesional cidofovir	12 mth	Complete response = 1, no response = 3

*Since last injection. Mth = months

Table 3. Summary of controlled trials or systematic reviews*

Author (year)	Study type	Study population	Adjuvant therapy	Outcome
Healy *et al.* (1988)	RCT	Aged <21 years, 123 patients	Systemic interferon	During first 6 mth, papilloma growth rate in IFN group was significantly lower than controls ($p = 0.0007$); this difference diminished during second 6 mth ($p = 0.68$)
Shehab *et al.* (2005)	Systematic review	Children & adults	Intralesional cidofovir	10 case series identified (86 patients). Complete response rate = 51%, partial response rate = 42%, no response rate = 7%
Chadha *et al.* (2012)	Systematic review (Cochrane)	Children & adults	1 intralesional cidofovir RCT identified	The included RCT showed no advantage of intralesional cidofovir over placebo at 12 mth
Soma *et al.* (2008)	Systematic review	Children & adults	Intralesional cidofovir	Multiple case series & case reports only. Small study populations. Complete response rates consistently reported as 60%

*These reviews do not relate specifically to children aged under three years. RCT = randomised, controlled trial; IFN = interferon

The following adjuvant therapies have been used in children who presented under three years of age: quadrivalent HPV vaccine, intralesional cidofovir, pegylated interferon, alpha-interferon, cimetidine and cetuximab.

Quadrivalent vaccine

The quadrivalent HPV vaccine (level 5 evidence) induces antibodies against HPV types 6, 11, 16 and 18. In July 2018, it was announced that this vaccine will be added to the UK vaccination programme for all children aged 12–13 years to protect against cervical and oropharyngeal cancers. This follows the vaccination programme already in place in other countries internationally.[22] Vaccination aims to generate immunity prior to HPV exposure and thus induce direct protection. There are no known adverse effects from the vaccine at present.[23]

Recurrent respiratory papillomatosis is principally caused by HPV types 6 and 11.[6] There are four case reports on use of the quadrivalent HPV vaccine in children with recurrent respiratory papillomatosis presenting under three years of age. Following three doses, three cases reported complete remission of papillomas at follow up.[24–26] One reported no therapeutic effect.[22] The proposed mechanism of action is unclear. It is hypothesised that vaccination causes sufficiently high antibody titres to prevent papilloma recurrence following surgical debulking.[27]

Intralesional cidofovir

Cidofovir (level 4/5 evidence) is a cytosine nucleoside analogue. It has antiviral activity against DNA viruses such as HPV. It has been the most widely used adjuvant treatment in recent years. Systemic treatment has been associated with severe adverse effects, including nephrotoxicity and neutropenia.[28] This has been evaluated by Naiman *et al.*, who investigated the systemic cidofovir levels following intralesional application and confirmed that the systemic levels are not high enough to cause toxicity.[29] Intralesional treatment has been associated with reports of oncogenicity in rodent studies.[14] In humans, there has been no correlation with adenocarcinoma as suggested in animal studies.[14,30] There have been reports of verrucous carcinoma in adults, which is argued to be HPV-related as opposed to being induced by cidofovir.[14] However, this requires further investigation with long-term follow up.

A systematic review by Soma and Albert identified complete response rates to intralesional cidofovir in children and adults to be approximately 60 per cent.[12]

We have identified 27 children who presented aged under three years who were treated with intralesional cidofovir. These data have been extrapolated from a number of case series and reports (Tables 1 and 2).[31–38] Five children (18.5 per cent) demonstrated complete response, 11 (40.7 per cent) demonstrated partial response and 11 (40.7 per cent) demonstrated no response. This indicates a variable response to intralesional cidofovir. None of these studies incorporated controls, and thus it is possible that the demonstrated response actually represents the natural history of the condition. Ksiazek *et al.* described a four-month-old child with laryngeal and pulmonary papillomas who demonstrated complete response to nebulised cidofovir.[39]

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It is important to note that the doses of intralesional cidofovir in these studies are highly variable. This aspect was reviewed by Clamp and Saunders in an attempt to determine a reasonable dosing consensus.[13] A response to their paper highlighted that because of the systemic effects of cidofovir, it is not licensed in many countries and therefore should be used with extreme caution.[40]

Alpha-interferon and pegylated interferon

Alpha-interferon (level 5 evidence) is a cytokine with antiviral and anti-proliferative properties. It was the initial adjuvant drug used for recurrent respiratory papillomatosis. Its use has largely ceased following a randomised controlled trial by Healy *et al.* in 1988, which showed an inadequate sustained response in 123 patients.[41] Recently, two treatment-resistant infants were treated with alpha-interferon, but neither demonstrated any reasonable improvement.[39,42]

Pegylated interferon is the novel counterpart. It increases the half-life of the drug, reduces immunogenicity and improves the pharmacokinetics. It is significantly more effective than alpha-interferon at treating hepatitis C.[18]

One case report is available relating to pegylated interferon.[18] A 14-month-old child with recurrent respiratory papillomatosis was treated with surgical debulking on a 2-weekly basis and required a tracheostomy. The child had no improvement with intralesional cidofovir and developed pulmonary papillomas at the age of three years. The child was intolerant to bevacizumab, and subsequent treatment with pegylated interferon reduced the need for surgical debulking to three-monthly. Unfortunately, because of deranged liver function this treatment was stopped.

- Juvenile-onset recurrent respiratory papillomatosis is more aggressive than the adult-onset form
- Recurrent respiratory papillomatosis presenting in those aged under three years represents the most aggressive form of the disease
- Several adjuvant therapies have been used to varying effect to reduce the burden of this disease and increase the interval between surgical debulking.
- The literature relating to management of infantile recurrent respiratory papillomatosis is based on case reports and small case series
- Quadrivalent human papilloma virus vaccine, intralesional cidofovir, pegylated interferon, alpha-interferon, cimetidine and cetuximab have been used in those presenting aged under three years

Cimetidine

Cimetidine (level 5 evidence) is an H_2 receptor antagonist most commonly used to reduce gastric acid secretion. At high doses, it has been noted to have immunomodulatory effects and therefore has been used for cutaneous warts.

One case report has shown a positive response in a child with treatment-resistant recurrent respiratory papillomatosis.[17] A five-month-old child presented with laryngeal papillomas, which rapidly progressed to the trachea, bronchi and lung parenchyma. A tracheostomy was inserted and regular surgical debulking was carried out by laser. Alpha-interferon, acyclovir and ribavirin were used without any convincing effect over a number of years. At age 10 years, the child underwent treatment with systemic cimetidine, and within 4 weeks had visible improvement in her airway, which has been sustained following cessation.

Cetuximab

Cetuximab (level 5 evidence) is an anti-epidermal growth factor receptor monoclonal antibody. Immunostaining has identified epidermal growth factor receptor-positive cells in 30 per cent of papilloma tissue.[9] On this basis, Loyo *et al.* used systemic cetuximab on an infant with laryngeal and tracheal papillomas.[9] The disease progressed despite this adjuvant treatment.

Conclusion

The literature relating to the management of infantile recurrent respiratory papillomatosis is based on case reports and small case series. The majority of papers relate to the successful use of adjuvant treatments, but it is likely that a number of failed treatments remain unreported. The natural history of recurrent respiratory papillomatosis results in spontaneous improvement following the development of immunity. It must be noted that the majority of current evidence does not include any control group to allow for spontaneous improvement. Similarly, several reports have combined adjuvant therapies, which hinders appropriate conclusions.

The decision to use adjuvant therapies must be based on current evidence in full knowledge of the risks and benefits – this must be individualised. None of the adjuvant treatments mentioned are licensed for treating recurrent respiratory papillomatosis. The rarity of the condition does not allow reasonable controlled studies to further evaluate this topic. Therefore, multicentre collaborations will be required to develop powered studies, which can produce valid conclusions and stronger evidence.

Competing interests. None declared

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