Recurrent Respiratory Papillomatosis

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14 Recurrent Respiratory Papillomatosis

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Key Points

- Recurrent respiratory papillomatosis (RRP) is a condition induced by human papillomavirus (HPV), characterized by recurrent growths of intraluminal papillomas in the airway.
- Patients present with dysphonia (both roughness and breathiness), coughing, and eventually airway obstruction.
- The disease can occur in both children and adults.
- The most common causative HPV types are HPV6 and HPV11.
- In the absence of a curative treatment, patients have to undergo frequent surgical treatment.
- Due to the debilitating and progressive nature of the disease, early recognition and treatment of the disorder are necessary.
- Introducing prophylactic vaccination against HPV6 and HPV11, as implemented in many countries, is critical to reduce the incidence of RRP.

14.1 Introduction

Recurrent respiratory papillomatosis (RRP) is a human papillomavirus (HPV)-induced disease characterized by recurrent growth of respiratory papillomas, mainly in the larynx. The most frequent causative types are HPV6 and HPV11. The condition can cause significant morbidity, can affect quality of life, and can be life-threatening. Correct diagnosis and treatment are therefore of great importance.

14.2 Epidemiology

There are two clinical presentations: juvenile-onset RRP (JoRRP), where the onset of disease is below the age of 12 years, and adult-onset RRP

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(AoRRP). These two types mainly differ in severity, with JoRRP being more aggressive.

The overall incidence and prevalence of RRP are similar in Europe, Africa, and South America (Table 14.1). AoRRP predominates in Europe, North America, and South America, as opposed to sub-Saharan Africa where JoRRP predominates (Tables 14.2 and 14.3) [1–18]. In Europe, there are three peaks in the incidence of the disease, at around 7, 35, and 64 years [19]. In sub-Saharan Africa, the last peak of AoRRP is absent, with a large peak at around 5 years and a smaller peak at around 45 years [3].

The incidence and prevalence of JoRRP in developing countries are similar to or slightly higher than that in developed countries (Table 14.2), but these data are probably underestimated for developing countries as patients often have symptoms that are not sufficiently severe to present or demise due to upper airway obstruc-

Table 14.1 Incidence and prevalence of recurrent respiratory papillomatosis

Region	Incidence per 100,000 population	Prevalence per 100,000 population per year
Funen and Jutland, Denmark (1965–1984) [1]	0.38	
United Kingdom (2014–2015) [2]		1.42
Free State, South Africa (2011–2015) [3]	0.51	1.39
São Paulo State, Brazil [6]	0.50	0.97

Table 14.2 Incidence and prevalence of juvenile-onset recurrent respiratory papillomatosis (JoRRP)

Region	Incidence per 100,000 children	Prevalence per 100,000 children per year
Funen and Jutland, Denmark (1965–1984) [1]	0.36	
Copenhagen, Denmark (1980–1983) [7]	0.6	0.8
Denmark (1974–1993) [11]	0.35	
Norway (1987–2009) [4]	0.17	
USA (1993–1994) [8]	4.3	
Atlanta and Seattle, USA (1996) [5]	0.12–2.13	1.00–3.97
USA (2006) [9]	0.51–1.03	1.45–2.93
Canada (1994–2007) [12]	0.24	1.11
Free State, South Africa (2011–2015) [3]	1.34	3.88
Lesotho (2011–2013) [10]	0.49	1.04
Japan [16]	0.1	
Thailand [16]	2.8	
Republic of Korea (2002–2015) [17]	0.3	
Australia (1998–2008) [15]		0.6–1.1
Australia (2000–2013) [13]		0.81
Australia (2012–2016) [14]	0.068	

Table 14.3 Incidence and prevalence of adult-onset recurrent respiratory papillomatosis (AoRRP)

Region	Incidence per 100,000 adults	Prevalence per 100,000 adults per year
Funen and Jutland, Denmark (1965–1984) [1]	0.39	
Copenhagen, Denmark (1980–1983) [18]	0.8	2.3
Norway (1987–2009) [4]	0.54	
USA [8]	1.8	
Free State, South Africa (2011–2015) [3]	0.18	0.38

tion prior to presentation. In Australia, the prevalence of JoRRP is lower than in other parts of the world, with an incidence that is declining following introduction of a HPV vaccination program including coverage of HPV6 and HPV11 [14].

14.3 Human Papillomavirus

Human papillomaviruses are non-enveloped DNA viruses that belong to the family *Papillomaviridae* [20]. The virion particle consists of a circular double-stranded DNA genome of approximately 8000 base pairs [20]. The HPV genome is divided into three regions, the long control region (LCR), early region (E1, E2, E4, E5, E6, and E7), and late region (L1 and L2) [20]. Expression and replication of the viral genes are controlled by E1 and E2 genes, while the E6 and E7 genes induce cellular proliferation, downregulate the tumor suppressors p53 and pRb, and influence the immune response by affecting several immunological pathways.

Classification of HPVs is based on the nucleotide sequence of the L1 gene, the most conserved region of the viral genome, with the L1 gene of different HPV types having less than 90% similarity [21]. Over 220 human papillomavirus (HPV) types have been identified [22]. RRP is caused mainly by HPV6 and/or HPV11 [14, 16, 23–33], the same HPV types that cause genital warts, although other types have been implicated in some studies [28, 32–34].

Variants of an HPV type have less than 2% similarity in the L1 gene [21]. Intratypic variants of HPV6 and HPV11 vary by geographic area but are not as geographically restricted as high-risk types [35–37].

14.4 Immune Response

HPV interferes with innate immunity and skews the adaptive immune response to a Th2-like or T-regulatory cell phenotype, instead of a more effective Th1-like response [38]. The change in immune response causes a virus-friendly cell environment, which allows the virus to evade normal clearance. Patients with RRP seem to be more prone to this change in immune responsiveness. HLA gene patterns and innate immune cell receptor expression have shown to differ between the general population and patients with RRP [39].

14.5 Etiology

HPV transmission in JoRRP is believed to occur during birth as the fetus passes through an infected birth canal. Primigravidae are more likely to have a long second stage of labor with prolonged exposure of the baby to HPV in the birth canal, leading to a higher chance of infection in the first-born child. While a minority of mothers of children with RRP have a history of genital condylomata, most have histological evidence of HPV infection [40].

In AoRRP, HPV infection is believed to be sexually transmitted, but may also be as a result of infection acquired at birth remaining latent until adulthood [41]. Activation of latent viral infection as a result of age-associated loss of immunity has been suggested for the last age group [19].

Papillomata occur mainly at sites at which ciliated and squamous epithelia are juxtaposed [42]. Squamous metaplasia following surgical trauma results in new iatrogenic squamociliary junctions being created. Tracheotomy also causes iatrogenic squamociliary junctions and often results in papillomata surrounding the tracheotomy opening and tip of the cannula.

14.6 Clinical Presentation

Patients with JoRRP usually present between the ages of 2 and 9 years, but cases with papillomata in the neonatal period have been described, and some patients may present as teenagers with symptoms for many years [3–5, 11–14, 32, 43, 44]. Boys and girls are equally affected.

The first symptom is progressive dysphonia, followed by stridor and difficulty with breathing. Recurrent upper respiratory tract infections, chronic cough, and hemoptysis are other symptoms

that may occur. Patients are frequently misdiagnosed as having asthma, laryngotracheobronchitis, foreign body aspiration, or laryngomalacia. In developing countries, patients often present with a history of hoarseness for many years and upper airway obstruction as a result of the poor availability and accessibility of healthcare services. In rare cases, pulmonary hypertension and cor pulmonale may occur as a complication of chronic upper airway obstruction [45].

Patients with AoRRP usually present with progressive dysphonia (both roughness and breathiness) or cough and rarely with dyspnea. In rare cases, sore throat is an initial symptom.

Patients from the first adult peak usually present in their late twenties to thirties. Often there is persistent dysphonia after a specific provoking incident. The second peak of AoRRP is in the early sixties. These patients often have no provoking incident. RRP may even be an incidental finding during intubation, without the patient having any complaints. Males are more commonly affected than females [4, 41].

The larynx is the most frequently affected site, with the trachea being the most common site of extralaryngeal involvement. Other extralaryngeal sites that may be involved include the nose, nasopharynx, oral cavity, oropharynx, and lungs. Extralaryngeal spread is significantly more common in patients with HPV11 disease [46]. Malignant transformation is rare but may occur in both laryngeal and pulmonary papillomas. The absence of HPV in the papillomata has been associated with malignant transformation with AoRRP [47].

14.7 Diagnosis

All patients with progressive or persistent hoarseness, stridor, and/or respiratory distress should undergo flexible laryngoscopy or direct laryngoscopy and biopsy [48]. The papillomata are recognizable as exophytic, pedunculated, or lobulated masses which may be single or multiple (Fig. 14.1). Histologically, the papillomata are exophytic finger-like protrusions of keratinized squamous epithelium overlying a layer of connective tissue stroma, with basal cell layer hyperplasia and abnormal keratinization (Fig. 14.2). Inspection of the airway should be extended up to the carina during the first surgery so that distant extension of papillomata can be found early and treated. Use of narrow-band imaging (NBI) can be very helpful in discerning the lesions (Fig. 14.3) [49]. Tumor evaporation by laser is not recommended at the first surgical

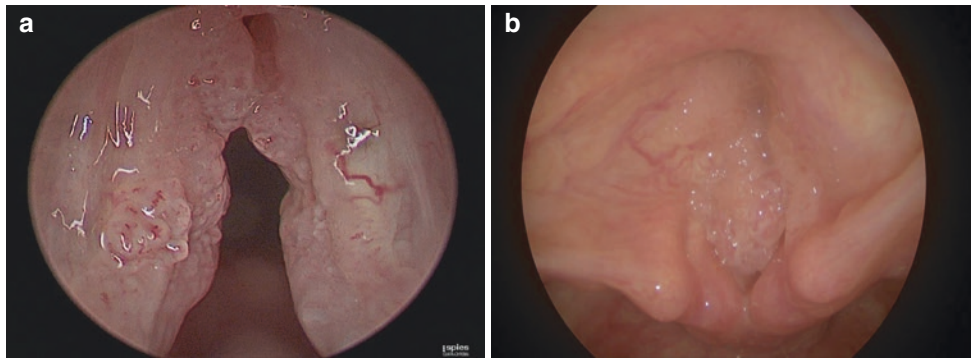


Fig. 14.1 Variety of perioperative laryngeal images of patients suffering from recurrent respiratory papillomatosis, with papilloma growth in different (supra)glottic locations and severity. Age and gender of patients shown in figure. (**a**) A 9-year-old female. (**b**) A 10-year-old female. (**c**) An 18-year-old female. (**d**) A 25-year-old female. (**e**) A 45-year-old female. (**f**) An 11-year-old male. (**g**) A 15-year-old male. (**h**) A 16-year-old male. (**i**) An 18-year-old male. (**j**) A 29-year-old male. (**k**) A 33-year-old male. (**l**) A 48-year-old male. (**m**) A 61-year-old male. (**n**) A 66-year-old male

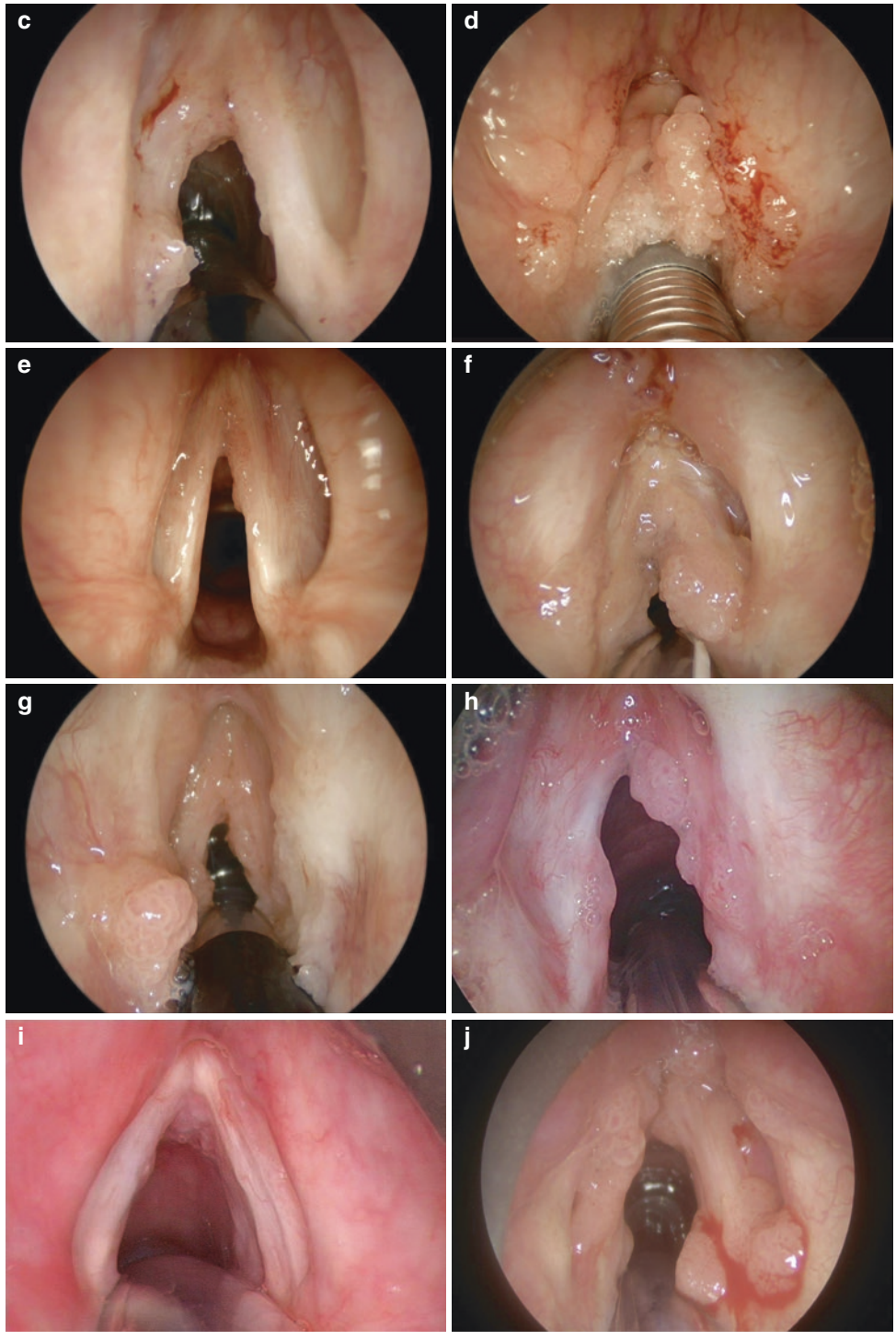
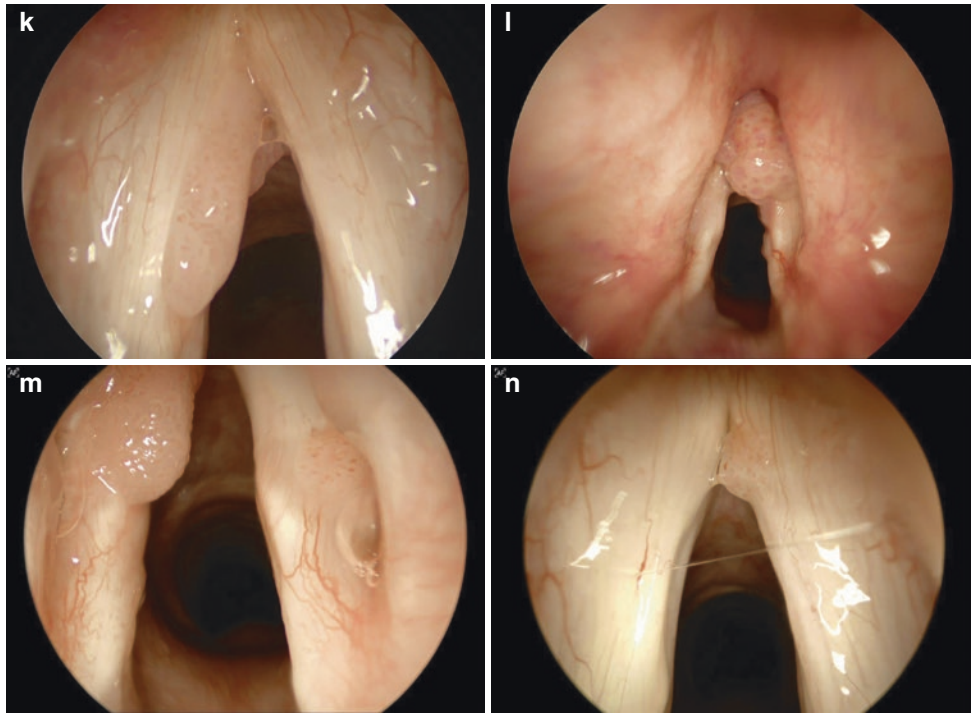


Fig. 14.1 (continued)



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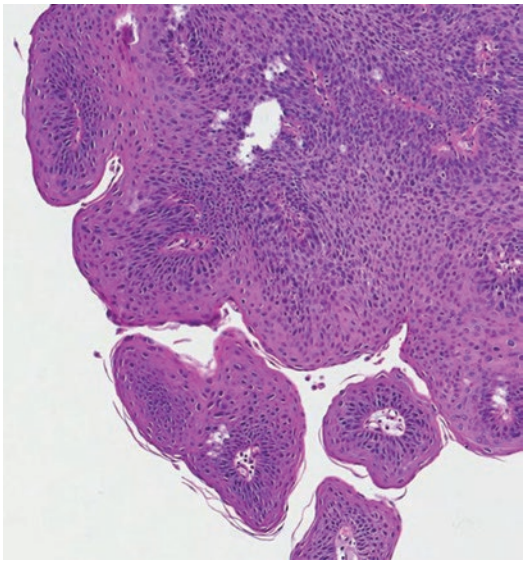

Fig. 14.2 Histological section (HE staining, original magnification 100×) of biopsy of recurrent respiratory papilloma of right true vocal cord. There are conspicuous finger-shaped protrusions that are cut transversely

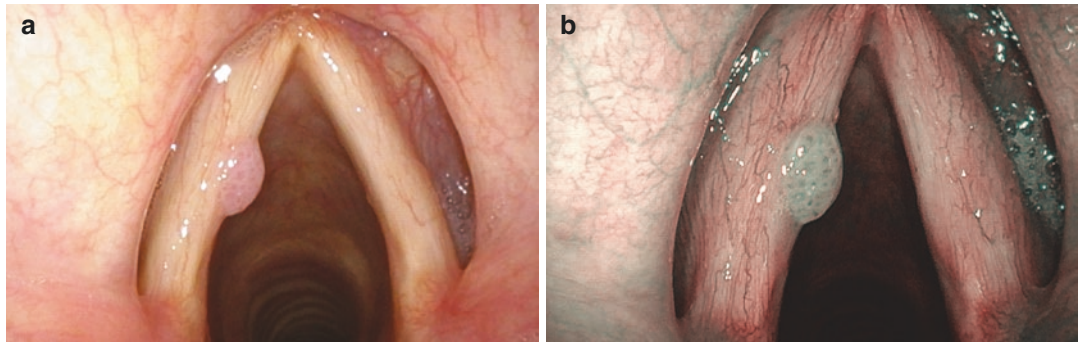

Fig. 14.3 Laryngeal papilloma (**a**) without narrow-band imaging and (**b**) with narrow-band imaging

procedure as tissue should be collected for histological examination and HPV typing. An early laryngeal carcinoma may macroscopically appear similar to papilloma. Chest imaging by either chest X-ray or CT scan should be performed in patients with pulmonary symptoms or signs, although CT scanning in all patients is being advocated [50].

14.8 Clinical Course

The clinical behavior of RRP is variable and unpredictable. In most patients, the frequency of surgery decreases over time, but in about one-third of cases, the surgical frequency remains constant or increases [11, 12, 15, 26, 46, 48, 51]. Although the disease eventually goes into remission in the most patients, some may have active RRP for many years. Recurrence may occur after many years of remission as the latent viral infection persists in the laryngeal tissue [46]. At least 50% of children with RRP require more than ten surgical procedures to control their disease, and 4–7% of all patients undergo more than a hundred procedures in their lifetime [46].

14.9 Quality of Life

The recurrent and persistent nature of the disease, need for frequent surgery, and dysphonia adversely affect the quality of life (QoL) of patients and place a significant social burden on the families of affected children [27, 52, 53]. In comparison with controls, adult RRP patients have more voice problems and a lower general health perception and are anxious [52]. Although all patients are more prone than average to depression and anxiety, older women suffer the most. Voice handicap has been found to be associated with smoking [52]. Screening for RRP-related psychosocial, practical, and medical problems that might be overlooked in normal outpatient clinic visits has been shown to significantly improve distress [54].

14.10 Staging

Several disease scoring systems have been proposed [25, 55, 56]. The most commonly used scoring system is the Derkay scoring system (Fig. 14.4) [56]. This system encompasses both a functional assessment of the patient, in which the severity of the hoarseness and degree of airway obstruction are assessed, and an anatomical assessment of the extent of disease. The respiratory tract, including the larynx, is divided into anatomical subsites, and all areas are scored based on the size of the papillomata on a scale 0–3. Scoring is difficult to carry out retrospectively as symptoms and extralaryngeal papillomata are also scored, but this staging system is widely used on a prospective basis.

Clinical score:

Describe the patient's voice today:	Normal(0) / Abnormal(1) / Aphonic(2)
Describe the patient's stridor today:	Absent(0) / With activity(1) / At rest(2)
Describe the urgency of today's intervention:	Scheduled(0) / Urgent(1) / Emergent(2)
Describe today's level of respiratory distress:	None(0) / Mild(1) / Moderate(2) / Severe(3) / Extreme(4)

Total clinical score:_____

Anatomical score:

For each site, score as: 0=None, 1=Surface lesion, 2=Raised lesion, 3=Bulky lesion

Larynx:

Epiglottis	Lingual surface:_____	Laryngeal surface:_____
Aryepiglottic folds	Left:_____	Right:_____
Arytenoids	Left:_____	Right:_____
True Vocal Cords	Left:_____	Right:_____
False Vocal Cords	Left:_____	Right:_____
Anterior commissure:_____		
Posterior commissure:_____		
Subglottis:_____		

Trachea:

Upper one-third:_____		
Middle one-third:_____		
Lower one-third:_____		
Bronchi	Left:_____	Right:_____
Tracheostomy stoma:_____		

Other:

Nose:_____
Palate:_____
Pharynx:_____
Oesophagus:_____
Lungs:_____
Other:_____

Total anatomical score:_____

Total score (Total clinical score + Total anatomical score):_____

Fig. 14.4 The Derkay staging system for recurrent respiratory papillomatosis [56]

14.11 Disease Severity

Involvement of multiple levels of the larynx or, specifically, of the subglottis at initial presentation is associated with more severe disease [57]. Histologically, the presence of atypical mitoses and of mitoses above the basal cell layer of the epithelium has been associated with more severe disease, but no such association has been found with the degree of dysplasia [58].

Most studies have found that patients with HPV11-induced RRP have more aggressive disease than those with HPV6-induced RRP [25–28, 46]. HPV typing is therefore a possible tool to detect disease aggressiveness [46, 59]. However, younger age at diagnosis is also associated with more aggressive disease and has been found to be a more significant marker of aggressiveness than HPV type [30, 46].

The possible role of intratypic variants in differences in severity of respiratory papillomatosis is unclear. Although functional differences have been found between intratypic variants of HPV6 and HPV11 [60, 61], there does not appear to be a difference in disease aggressiveness between variants of a particular HPV type [62].

A maternal history of condyloma acuminata appears to be associated with more aggressive JoRRP [30, 40]. Gastroesophageal reflux disease and asthma have previously been suspected to be associated with aggressive disease, but this has not been shown to be the case [46, 63].

14.12 Surgery

As there is no cure, treatment consists of repeated microlaryngoscopic procedures to remove the papillomata while maintaining the normal laryngeal tissue until the patient goes into remission. The goal of surgical interventions should not be to remove all visible papillomata. Even if they are all removed, the disease is expected to recur as HPV DNA is found in the adjacent macroscopically uninvolved laryngeal tissue and other adjacent anatomical sites. Removal of the papillomata is performed using various methods, such as cold steel instruments, microdebrider, laser (CO_2, KTP, or pulse dye laser), or coblation, depending on surgeon's preference and availability of equipment [48]. The use of a laser or microdebrider has not been associated with a longer intersurgical interval, while treatment with the microdebrider may result in a better voice outcome compared with the CO_2 laser [64].

It may be necessary to stage surgical interventions, in order to prevent synechia formation in the anterior commissure. In the authors' experience, a 6-week interval between surgeries on the two sides of the anterior commissure seems to be sufficient.

Further procedures are performed based on the severity of the disease of an individual patient. A watchful waiting policy should be considered in the absence of voice or airway complaints.

Laryngeal complications such as anterior commissure synechiae, scarring of superficial vocal cord epithelium on the underlying layers, ventral glottic stenosis, dorsal glottic stenosis, and granuloma formation from repeated surgical procedures are common [31]. These complications result in abnormal voice quality in the long term, with a higher number of surgical procedures correlating with the development of complications and poorer voice quality [15, 64, 65].

A tracheotomy may be required for patients with airway obstruction. The presence of a tracheotomy has been associated with possible spread of papillomata to the trachea and lower airways, but this view is controversial. Tracheotomies are usually for patients with the most aggressive disease, who may develop distal spread regardless of whether or not they had a tracheotomy [31, 48]. The tracheotomy rate in developed countries is generally low, but is much higher in developing countries, mainly because the expertise to manage patients with RRP is not as readily available.

14.13 Adjuvant Treatment

Adjuvant treatments that have been used in RRP include indole-3-carbinol, mumps vaccination, MMR vaccination, HPV vaccination, interferon-α, bevacizumab, cidofovir, programmed cell death protein 1 (PD-1 inhibitors),

and celecoxib. The highly variable disease course makes it difficult to determine the effectiveness of these treatments. Use of programmed cell death protein 1 (PD-1), celecoxib, and heat shock protein E7 is no longer recommended in the treatment of JoRRP [48].

Cidofovir and bevacizumab are mainly used as intralesional therapies. Cidofovir is a cytosine nucleotide analog that blocks DNA virus replication by inhibiting viral DNA polymerase. Several uncontrolled and retrospective studies have shown that intralesional cidofovir is effective for RRP with about 40–50% of patients achieving remission [55, 66]. However, a systematic review of adjuvant antiviral therapy for the treatment of RRP identified only one randomized, double-blind, placebo-controlled trial of intralesional cidofovir administered at the time of surgical debulking that showed significant clinical improvements in both the cidofovir and placebo groups and no significant difference between the two groups [66, 67]. It would be extremely difficult to perform a large prospective randomized trial of intralesional cidofovir because of the small number of patients.

Bevacizumab is a recombinant human monoclonal antibody that blocks angiogenesis by binding to human vascular endothelial growth factor A (VEGF-A) [68]. Intralesional bevacizumab has been shown to extend the intersurgical interval in small series, while systemic bevacizumab has been shown to be of benefit in case studies of patients with severe RRP [68, 69]. However, systemic use of bevacizumab might become the treatment of first choice [70, 71].

Of the three HPV vaccines available in 2022, the bivalent vaccine (Cervarix®), the quadrivalent vaccine (Gardasil®), and the nonavalent vaccine (Gardasil® 9), two (Gardasil® and Gardasil® 9) protect against HPV6 and HPV11. In Australia, a significant decrease in the incidence of JoRRP was observed following the introduction of a national vaccination program with a high uptake using the quadrivalent HPV vaccine in 2007 [14]. This is probably due to the decreased prevalence of HPV6 and HPV11 genital infection in the Australian population resulting in a reduction of intrapartum transmission of the virus [14]. There were no new cases of JoRRP reported in Australia in 2018 and 2019 [72]. The introduction of vaccines that are protective against HPV6 and HPV11 would probably have a greater impact in regions with a higher incidence of JoRRP.

Although these are prophylactic vaccines, they have also been used as adjuvant therapy for patients with RRP, mainly in adults. There are two proposed mechanisms of action: inhibition of latent HPV infection in the mucosa surrounding the surgical site by antibodies produced in response to the vaccine and activation of the cell-mediated response by the vaccine. A systematic review and meta-analysis found a statistically significant reduction in the mean number of surgical procedures per month after use of the HPV vaccine as a therapeutic agent [73].

14.14 Speech Therapy

Most patients have poor voice quality that can range from mild hoarseness to aphonia [52, 65]. While speech therapy can be used for most benign vocal cord abnormalities, surgery is the treatment of choice for dysphonia due to RRP. Speech therapy can be considered as complementary to surgery or if surgical options for a scarred larynx are not considered feasible.

14.15 Conclusion

RRP is a condition that initially manifests itself as hoarseness, but can lead to life-threatening obstruction of the upper airway. Treatment requires repeated surgical procedures as there is no cure.

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