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Long-term follow-up and outcome in patients with recurrent respiratory laryngeal papillomatosis

Eva Rye Rasmussen^{1*}, Didde T. Schnack^{1*}, Andreas Schjellerup Jørkov¹, Anna Axelsson Raja², Caroline Holkmann Olsen³ & Preben Homøe¹

ABSTRACT

INTRODUCTION: Recurrent respiratory papillomatosis is characterized by wart-like lesions of the upper airway and is most frequently caused by human papillomavirus (HPV). The disease has significant impact on quality of life due to potential airway obstruction, dysphonia and the need for serial surgeries. The main objective of this study was to describe patient characteristics and long-term follow-up data in a Danish cohort with the disease.

METHODS: The study was a longitudinal retrospective cohort-study using data from electronic medical records and a pathology database.

RESULTS: A total of 61 adult and four juvenile patients were identified. The male-to-female ratio was 2.4. In the adult population, the mean age at onset was 45 years. The median number of surgeries was four (interquartile range: 2-8). The mean follow-up time was 8.7 years (range: 7 days-30 years). Three cases of malignant transformation were observed. In the juvenile population, the mean age of onset was 8.5 years (range: 3-12 years). The mean follow-up time was 11.5 years (range: 2-23 years), and the number of surgeries per year at risk was one/year. CO₂-laser and microdebrider were the surgical techniques usually employed. 43% of histopathologic analyses could detect HPV infection (subtype 6 or 11).

CONCLUSIONS: More males than females suffer from respiratory papillomatosis; age of onset was either in childhood or in mid-life. Use of CO₂-laser or microdebrider was the preferred surgical approach in this cohort.

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TRIAL REGISTRATION: not relevant.

Recurrent respiratory papillomatosis (RRP) is mainly a benign chronic disease of viral aetiology affecting both children and adults. Juvenile-onset RRP (JORRP) is defined as disease before the age of 18 years of age and adult-onset (AORRP) as onset of disease at 18 years of age or later. The disease is characterized by wart-like lesions of the upper airway. The incidence is 0.17 per 100,000 for JORRP and 0.54 per 100,000 for AORRP [1]. RRP has three separate peaks in the distribution of age at onset; 7, 35 and 64 years [2]. The incidence of RRP has not increased over the past five decades [3].

RRP is most commonly caused by persistent infection of the respiratory epithelium by low-risk human papillomavirus (HPV) of subtypes 6 and 11. The onco-

genic HPV subtype 16 has also been identified in rare cases [4]. Dysplastic lesions in RRP occur in 10-55% of adult cases [5, 6]. Malignant transformation of RRP neoplasms occurs in up to 5% of AORRP, but is more rare in JORRP [3, 6].

RRP has significant impact on health-related quality of life (QoL) due to potential airway obstruction, dysphonia and the need for serial surgeries [6, 7]. In developing countries, up to 90% of paediatric RRP patients have an emergency tracheostomy performed [8]. There is no curable treatment for RRP, and repeated surgical procedures are required to control growth, improve voice quality and prevent respiratory obstruction. Adjuvant therapies have been used with variable success [9]. Studies of the quadrivalent HPV vaccine in the RRP population have shown conflicting results [10, 11].

New assessment and treatment modalities are currently being investigated [12]. The introduction of HPV vaccines in adolescents around the world may change the incidence and epidemiology of RRP.

The primary aim of this study was to describe patient characteristics and long-term follow-up data, focusing on repetitive surgery in a Danish cohort with RRP. The secondary aims were to assess the differences in surgical approach in our department and to describe a population of RRP patients before the introduction of the HPV vaccination in Denmark.

METHODS

Study population and design

The study was a retrospective longitudinal cohort-study based on evaluation of medical records and pathology archives of RRP patients. Patients were included if they had been treated for RRP at the Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital between 1 January 2004 and 31 May 2014.

The population was divided into two groups based on data completeness. Medical records and histopathological analyses were available for patients diagnosed at our own department during the study period (Group 1). Baseline, procedural and histology data for patients diagnosed and/or treated elsewhere prior to 2004 and subsequently treated at our institution (Group 2) were less complete.

ORIGINAL ARTICLE

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FIGURE 1

Risk of recurrence over time in adult-onset recurrent respiratory papillomatosis patients operated with either CO₂-laser or microdebrider.

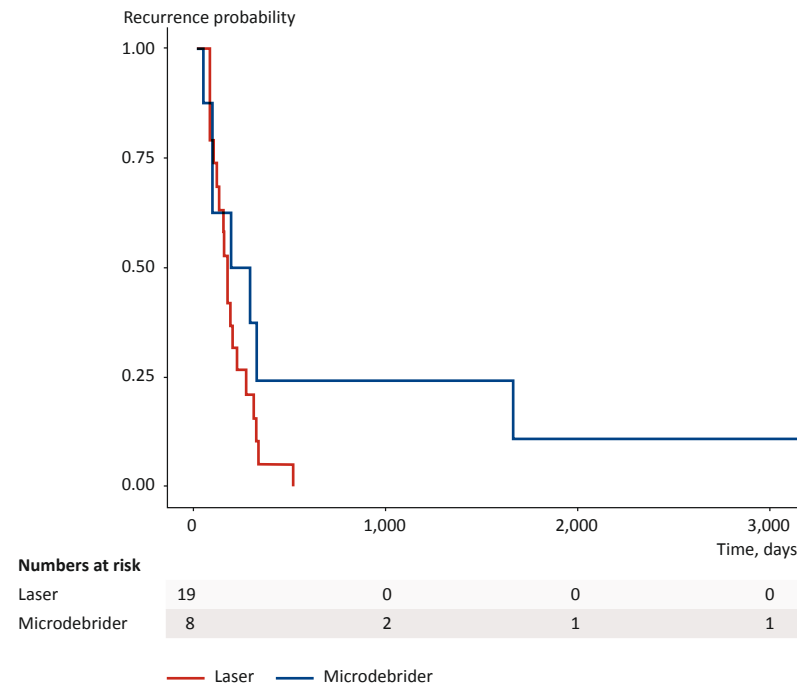


TABLE 1

Baseline data for juvenile-onset recurrent respiratory papillomatosis patients (N = 4).

Age at disease onset, yrs, mean (range)	8.5 (3-12)
Male:female, n	1:3
Total follow-up time, yrs	46
Follow-up time, yrs, mean (range)	11.5 (2-23)
Surgical procedures, n, total, mean [median]	46, 11.5 [6]
Surgical procedures/yrs at risk ^a , n	1

a) Yrs at risk = yrs after diagnosis when a patient is "at risk" of further surgery.

To identify patients with RRP, medical records and pathology archives were reviewed. The International Code of Disease version 10 (code DD14.1) neoplasma benignum laryngis was used to search the medical record system. Patients were also retrieved by a search in the Danish Systematized Nomenclature of Medicine "SNOMED" pathology registry using the diagnoses; papilloma, light koilocytotic atypia, squamous cell papilloma, invert papilloma, papillomatosis and polyps, HPV type 6, HPV type 11, HPV. Searches were combined with localization to the larynx. Medical records were reviewed to extract clinical data, including age, gender, age of disease onset, date of first surgery, total number of surgeries and last date of follow-up. For patients diag-

nosed before 2004, onset of disease was defined as the first date a histopathologic analysis was performed since the real date of diagnosis was not available.

Only four patients with JORRP were identified. They were omitted from the statistical analyses and are described as a separate entity.

Ethics

The study was approved by the Danish Health and Medicines Authority and by the Danish Data Protection Agency (record number 2015-41-3829) as appropriate.

Statistical analysis

Statistical analysis was performed using SAS version 9.4 (Cary, NC, USA). Normally distributed data (age, follow-up time) are presented as mean \pm standard deviation (SD) or mean (range) and non-normally distributed data (number of procedures) as median (interquartile range (IQR)). Between-group differences for normally distributed variables (i.e. age) were evaluated using the unpaired Student's t-test. For non-normally distributed continuous variables, we used the Wilcoxon rank sum test. Comparison of categorical variables was done with the chi-squared test or Fisher's exact test, when appropriate. Correlation was evaluated using Pearson's correlation coefficient. A p-value < 0.05 was considered statistically significant. 95% confidence intervals (CI) are reported where appropriate. "R" (an open source software environment for statistical analysis) was used to produce Figure 1.

Trial registration: not relevant.

RESULTS

Baseline data

A total of 65 patients with RRP were identified: 61 patients (Group 1: 30 and Group 2: 31 patients) with AORRP and four with JORRP (Table 1). Among the adult patients, 49% were diagnosed at Zealand University Hospital in the 2004-2014 period (Group 1). The male-to-female ratio was 2.4. The mean age at onset for AORRP was 45 years (SD: ± 15 years). The follow-up time varied considerably between Group 1 (mean = 1.9 years, range: 7 days-9.5 years) and Group 2 (mean = 15.5 years, range: 1 month-30 years). Thus, the number of surgical procedures also varied between the groups with a mean of two procedures for Group 1 and a mean of eight procedures for Group 2.

In the overall AORRP group, there was no significant gender difference for age of onset. However, in the group of patients diagnosed prior to 2004 (Group 2) compared with Group 1, men were significantly older (mean = 48 ± 16 years) at onset than women (mean = 35 ± 10 years), $p = 0.02$; 95% CI: 2-24 years.

Surgical data

Reliable data for AORRP localization, surgical technique and histopathology were available only for surgical procedures in patients belonging to Group 1 (Table 2).

Therefore, Group 2 was excluded from the analyses below.

Surgical technique

All 72 procedures in Group 1 were performed using microlaryngoscopy with biopsy under general anaesthesia. Surgical details are summarized in Table 2. CO₂-laser evaporation was primarily used as surgical technique in the study period; but in 2012, the surgical microdebrider (Medtronic, Minneapolis, USA) was introduced at our department and became popular. One surgery was performed using the coblation (Smith&Nephew, London, UK) technique. Figure 1 illustrates number of surgical procedures with laser (red) or microdebrider (blue) and time to recurrence.

Localization of primary papillomatous lesion

Single-sided papillomatosis was found in 23 patients (76.7%), with a predominance of left-sided disease (60.9%). In all, 22 of 30 patients had affection of one or both vocal cords (73.3%), whereas supra- and subglottic localization (four and two patients respectively) was more rare (Table 2). The remaining two patients had multifocal disease of the larynx (both with involvement of the vocal cords).

Histopathology

Out of the 72 procedures in Group 1, the tissue was submitted for histology in 54 (75%) procedures (30 patients); and among these, 21 (39%) specimens were assessed for HPV risk status (Table 2).

Three patients in Group 1 (10%), all of whom were tobacco users, were diagnosed with carcinoma. The first patient with malignancy was a 55-year-old male. During the first procedure, squamous cell papillomas were found. Due to clinical suspicion of malignancy, a second procedure was performed and histopathological analysis showed verrucous carcinoma. Since the tumour invaded a lymph node, it was classified as stage T2N1M0, but the node stage was doubtful as it was diagnosed only by computed tomography and not seen on prior magnetic resonance imaging. The second patient was a 50-year-old male. Histopathology from the sixth surgery showed squamous cell carcinoma. The last patient with malignant transformation was a 36-year-old male who had severe dysplasia at the first surgery, and histopathology from the second procedure two months later revealed squamous cell carcinoma. All three patients were referred for oncologic treatment and follow-up.



TABLE 2

Localization, surgical technique, histopathology and human papillomavirus (HPV) status in Group 1 patients.

	Patients, n	Surgical procedures, n (%)
<i>Localization of papilloma</i>		
Side:		
Left side	14	–
Right side	9	–
Bilateral	7	–
Total	30	–
Anatomical site:		
Glottis	22	–
Supraglottic	4	–
Subglottic	2	–
Multiple sites	2	–
Total	30	–
<i>Surgical technique^a</i>		
CO ₂ -laser	–	32 (44.4)
Microdebrider	–	15 (20.8)
CO ₂ -laser and microdebrider	–	1 (1.4)
Coblation	–	1 (1.4)
Biopsy only	–	25 (34.7)
Total	–	72 (100)
<i>Histopathology^b</i>		
Benign papillomatosis	–	51 (94.4)
Squamous cell carcinoma	–	2 (3.7)
Verrucous carcinoma	–	1 (1.8)
Total	–	54 (100)
<i>HPV status^c</i>		
HPV low risk type 6 or 11	–	9 (42.9)
No evidence of HPV	–	8 (38.1)
P16 negative	–	4 (19.0)
Total	–	21 (100)

a) Data available for 72 procedures in 30 patients (Group 1).

b) Data available for 54 surgical procedures.

c) Data available for 21 of 54 histopathological analyses.

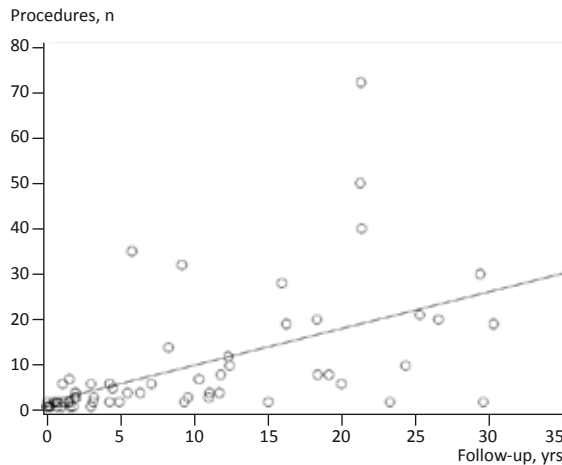
Long-term follow-up

Overall, AORRP patients (Group 1 and Group 2) were followed-up for 8.7 years (range: 7 days-30 years) and underwent a median of four (IQR: 2-8) surgical procedures. As expected, a significant correlation was observed between follow-up time and number of procedures ($r = 0.55$; $p < 0.0001$) with an event rate of 1.05 procedures per year of follow-up, as shown in Figure 2. No significant correlations were observed regarding age or gender distribution. Figure 1 shows the correlation between time to recurrence and surgical method (laser or microdebrider). No difference was noted between the two methods.

Five patients (mean age = 44.6 years, two women and three men) underwent more than 30 procedures each. Two patients were subsequently vaccinated with the quadrivalent HPV vaccine, but no effect on recurrence was noted.

FIGURE 2

Correlation between number of surgical procedures and years of follow-up. The longer a patient has suffered from recurrent respiratory papillomatosis, the more surgeries he or she has endured.



Juvenile-onset recurrent respiratory papillomatosis

The group of patients with JORRP consisted of one boy and three girls (Table 1): The boy was a three-year-old who underwent at least ten surgeries during a 12-year follow-up period. He was hereafter referred to another hospital due to web formation. The first girl was 11 years old when diagnosed; she had two surgical procedures performed during 23 years of follow-up. The second girl was diagnosed at 12 years of age and underwent 32 surgeries during a nine-year period. The third girl was diagnosed at eight years of age and had two surgical procedures performed during a two-year follow-up period.

No serious complications were registered in patients treated for AORRP or JORRP; except from voice alterations, the most common side-effects of surgery were scar tissue and web formation in the anterior commissure of the larynx. Laryngeal stenosis did not occur. None of the children have received HPV vaccination.

DISCUSSION

In this long-term follow-up study of children and adults with RRP, we found a mean age of onset of AORPP of 45 years and JORRP of 8.5 years, which is a slightly later than reported in a Danish cohort of CO₂-treated RRP patients [13]. A male predominance has previously been reported by others [1, 13, 14]. During a mean 8.7 years of follow-up in the AORRP population, patients underwent a median of four procedures, which concurs with previous findings [13]. In three (10%) of 30 patients for whom histopathology reports were available, the papillomas underwent malignant transformation over time. A significant correlation between follow-up time and

number of surgical procedures was shown (Figure 2). This is consistent with previous studies [6, 15]. However, significant differences in follow-up time and number of procedures were observed between the two groups of our study. In Figure 1, the surgical approach was presented as a function of time and probability of recurrence. Unlike previous studies, no significant difference between the two modalities was noted [16]. However, the number of surgical procedures with the microdebrider was limited and this indicates a potentially low sample-size bias.

The JORRP population consisted of four children/adolescents. The range in number of surgical procedures was large (2-32). Chadha et al found a median onset of disease age of 3.8 years [17]. Karatayli-Ozgursoy et al also found a much lower age of onset in their population [6]. The incidence of surgeries in JORRP patients in the two studies was higher than in our study; probably due to a lower age of onset.

In the present study, no adjuvant therapy was used, but cidofovir injected at 2-4 week intervals has been proven efficient [18, 19]. Other adjuvant therapies (mumps vaccine, interferon, other antiviral agents, cis-retinoic acid and more) have been employed with variable success, but none have proven universally applicable for RRP [9]. Future therapies like a recombinant fusion protein of *Mycobacterium bovis* heat shock protein 65 and E7 protein from HPV-16 and photodynamic therapy have shown promising results [9].

The potential effects of HPV vaccines may be divided into two types. One type would be the effect of routine vaccination and the other would be vaccination after the RRP diagnosis. The implementation of HPV vaccines worldwide could decrease the incidence of RRP. In Denmark, HPV typing is now standard in RRP patients, and this may influence decision-making on HPV vaccination in the affected children. Until 2015, the vaccine was the quadrivalent Gardasil (subtypes 6, 11, 16, 18), but it has been changed to the bivalent Cervarix (16, 18). Boys are not offered this vaccination in Denmark.

Surgical removal, preferably using narrow-band imaging, is still the gold standard for all RRP patients [20]. The most common complications to RRP surgery include hoarseness, synechias, stenosis and scarring due to recurrent surgery. In our material, there has been a shift from CO₂-laser treatment to microdebrider/shaver treatment. We were unable to draw any firm conclusions based on this shift since the latter modality was only recently introduced in our department. However, it is the perception of the surgeons that usage of the microdebrider is easy and causes less scar tissue. Furthermore, with the microdebrider it is easier to see when healthy tissue is reached, since it does not burn the tissue like the laser. Also, the microdebrider can more easily re-

move papillomas on the inferior part of the vocal cords, unlike the laser where the beam needs bending using a mirror, or the surgeon must apply much traction to the tissue to reach the necessary position [9]. Other studies have also documented fewer recurrences and sequelae in patients treated with microdebrider [9, 13, 16]. Randomized controlled trials are lacking.

Prior studies have shown a decreased QoL in both JORRP and AORRP patients equal to that encountered in other severe diseases such as cystic fibrosis and depression [3, 6, 17]. Close observation of both young and adult RRP patients is advised in order to manage their physical disease and to assess the psychological aspects of RRP. Guidelines concerning follow-up time and time intervals between visits in relapse-free patients are missing.

Establishment of nationwide or international databases for RRP patients could increase the knowledge base, create a basis for quality assessment between treatments and between departments and stimulate unification of the treatment offered to RRP patients.

CONCLUSIONS

Young and middle-aged men were most prevalent in the cohort. Left-sided papillomatosis involving the vocal cords was most common. Most patients need multiple surgical procedures over time due to recurrent disease. HPV typing in all RRP patients is of interest for future decision-making on adjuvant therapy, i.e. HPV vaccination. We suggest creation of a nationwide database to increase evidence-based research.

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