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Original article

Risk factors for severity of juvenile-onset recurrent respiratory papillomatosis at first endoscopy



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ABSTRACT

Objective: The study objective was to determine risk factors for severity of juvenile-onset recurrent respiratory papillomatosis (RRP) at first endoscopic evaluation.

Methods: Based on a review of all cases undergoing surgery for juvenile-onset RRP in two pediatric otolaryngology departments in the USA and France, the following severity risk factors were analyzed: number of laryngeal levels involved, extension to the subglottis, and bilateral involvement.

Results: Thirty-two patients were included, with 571 endoscopic procedures. Number of endoscopies per patient varied according to initial extension: 30.67 procedures when all three levels were involved, 15.57 procedures when two and 14.08 procedures when only one ($P=0.03$). The odds ratio for risk of >14 procedures in 3-level involvement was 20.43 ($P=0.047$). Initial subglottic extension tended to be associated with more endoscopic procedures (23.67 vs 15.56, $P=0.16$).

Conclusions: RRP severity correlated with initial laryngeal extension of papillomatous lesions at first endoscopy. This finding allowed a short 3-item assessment scale to be created for routine use, complementary to Derkay's assessment scale.

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1. Introduction

Juvenile-onset recurrent respiratory papillomatosis (RRP) is the most common benign childhood tumoral pathology of the larynx. Although benign, it is recurrent, often with airway spread [1]. It is aggressive in terms of recurrence and extension, although malignant transformation is rare.

One of the challenges is to predict progression and severity: there is a strong demand for this from patients and families, but which is hard to satisfy. According to the literature review by Niyibizi et al. of many studies seeking to identify risk factors for progression and severity, those most frequently reported were young age at onset and HPV-11 infection [2]; others are controversial.

Macroscopic extension on first endoscopy might be a predictive factor but to our knowledge has never really been explored in relation to severity of RRP [2].

The tools currently used to assess extension comprise scales and scoring systems. Several have been used but none were consensual until 1998 when Derkay published a clinical and laryngoscopic staging scale which is now the most widely used by ENT physicians dealing with RRP [3]. It comprises both clinical functional assessment and anatomic assessment of disease spread, the latter dividing the aerodigestive tract into 25 sites, each scored 0–3 for presence or absence of papillomatous lesions: 0 = no lesion; 1 = surface lesion; 2 = raised lesion; and 3 = bulky lesion. Maximum score is thus 75. In 2004, another publication from the same team predicted inter-procedure intervals, using the scale in 17 patients [4]. In our own experience, certain location factors (e.g., subglottic, multi-level or bilateral lesions) show particular risk of severity or progression, but the scale's global score is uninformative regarding these locations.

The aim of the present study was to identify risk factors for severity of juvenile-onset RRP on first endoscopy, on data from two pediatric ENT departments, one in the USA and one in France, with a view to creating a simple assessment scale.

2. Materials and methods

All new cases of RRP treated in the pediatric ENT departments of the University of Iowa Hospitals and Clinics (Iowa, USA) and La

Abbreviations: RRP, Recurrent Respiratory Papillomatosis.

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Table 1
Demographic and surgical data for patients treated for juvenile-onset recurrent respiratory papillomatosis in the 2 study centers.

	2 centers	UIHC	LTCH	P
Number of patients	32	20	12	
Female	19	12	7	
Male	13	8	5	
Age at first endoscopy (years)				
Min	0.57	0.57	0.64	
Max	14.55	14.55	12.16	
Mean	5.33	5.02	5.86	0.66 ^a
Standard deviation	3.79	3.60	4.20	
Median	4.17	4.14	5.63	
Number of endoscopies				
Total	571	366	205	
Min	2	3	2	
Max	68	68	61	
Mean	17.84	18.30	17.08	0.56 ^a
Standard deviation	14.97	14.36	16.21	
Median	13.50	16.00	12.50	

UIHC: University of Iowa Hospitals and Clinics. LTCH: La Timone Children's Hospital, Marseille.

^a Mann-Whitney test.

Timone Children's University Hospital (Marseille, France) between January 1, 2000 and April 30, 2015 were included. Patient files and surgical reports were examined to collect demographic and treatment data. Demographic data comprised: gender, date of birth and date of diagnosis. Endoscopic data comprised: date of each procedure, number of procedures, results of last endoscopy, and HPV genotype. Data were collected and analyzed with precision and lesions were classified according to laterality (bilateral, left or right) and location, focusing on the laryngeal compartments involved, with 3 levels: supraglottic, glottis and subglottis. Patients with less than 1 year's follow-up were excluded.

Mean values with standard deviation and median values with range were calculated for continuous variables. Significance was assessed on multivariate analysis with logistic regression and Mann-Whitney test; the significance threshold was set at $P < 0.05$. Severity was assessed in terms of number of procedures and presence of papillomatous lesions on last endoscopy. The risk factors analyzed were macroscopic extension on first endoscopy: number of levels involved, subglottic or tracheal extension regardless of number of levels, and bilateral involvement.

The study had local IRB approval in line with US Department of Health and Human Services regulations (45 CFR 46). Under French law (article L1121-1, modified by article 5 of the Act n° 2011-2012 of December 29), review board approval was not necessary for this kind of study. The study adhered to the Declaration of Helsinki and French good practice guidelines.

3. Results

Thirty-two patients were included: 19 (59.4%) female, 13 (40.6%) male (Table 1). Mean age at first endoscopy, with or without treatment, was 5.33 years, with no significant difference between centers (5.02 and 5.86 years; $P = 0.48$). Twenty-three of the patients (71.9%) were under 7 years of age at diagnosis.

Patients underwent a total 571 endoscopic procedures, with a mean 17.84 (18.3 and 17.08 according to center; $P = 0.56$), for a maximum 68. On first endoscopy, all but 2 patients (93.8%) showed bilateral lesions. Twelve (37.5%) showed involvement of a single level, 14 (43.8%) of 2 levels and 6 (18.8%) of 3 (Table 2). All showed glottic lesions at diagnosis; 9 (28.1%) had subglottic lesions. All showed dysphonia at diagnosis, and 6 showed respiratory symptoms (stridor and/or dyspnea).

Table 2
Laryngeal papilloma location according to number of laryngeal levels involved: subglottis, glottis and supraglottic.

Number of laryngeal levels	n	Subglottis	Glottis	Supraglottis
1	12	0	12	0
2	14	3	14	11
3	6	6	6	6
Total	32	9	32	17

All patients showed glottic lesions. In 2-level involvement (14 patients), 11 patients had supra- and 3 sub-glottic lesions.

Mean follow-up was 6.02 years (range, 1.02–15.7 years; median, 4.66 years). There was no significant difference in follow-up according to initial extension ($P = 0.49$).

We were able to identify significant prognostic factors at initial assessment of RRP extension (Table 3). Patients with initial involvement of more than 1 level underwent more endoscopies: 30.67 if 3 levels, 15.57 if 2, and 14.08 if 1 ($P = 0.03$). Patients with initial 3-level involvement underwent a mean 30.67 endoscopies, versus 14.88 in 1- or 2-level involvement ($P = 0.01$). The odds ratio for > 14 endoscopies in case of 3-level involvement was 20.43 ($P = 0.047$). Whatever the number of levels involved, patients with subglottic extension tended to undergo more endoscopies: 23.67 vs. 15.56 ($P = 0.16$). The impact of bilateral involvement could not be assessed due to the small number of unilateral cases ($n = 2$). Age at diagnosis, gender and initial symptoms were not significantly associated with number of endoscopies.

At last follow-up, 17 patients were free of papillomatous lesions and 15 showed residual disease, without significant correlation with initial extension. Age at diagnosis, gender and initial symptoms were not significantly associated with residual disease on last endoscopy. HPV genotype was identified in 9 of the 32 patients: 8 HPV-6 and 1 HPV-6/16 co-infection.

4. Discussion

Initial papillomatous lesion extension was the main factor for severity in juvenile-onset RRP. Notably, 3-level involvement was associated with more than twice as many endoscopies: 30.67 vs. 14.88 ($P = 0.01$). Subglottic extension showed a trend as prognostic factor, although significance could not be demonstrated (23.67 vs 15.56 endoscopies; $P = 0.16$).

Juvenile-onset RRP is a childhood disease classically diagnosed at 2–6 years of age, with balanced sex ratio [5]. 19 female and 13 male children were included in the present study (F/M sex ratio, 1.46:1), with a mean age at diagnosis of 5.4 years, and 23 of the 32 patients aged <7 years at diagnosis. The natural history of HPV infection accounts for the delay between infection (probably post-partum) and symptom onset. Progression is highly variable, but shows 3 phases: (1) latency phase; (2) development of papillomas; (3) persistent infection sometimes progressing to high-grade dysplasia [6]. Unlike adult RRP, the juvenile form rarely shows malignant transformation, but propagates mainly in the airway, with frequent recurrence [7]. The vocal folds are the origin in most cases, as in all cases in the present series. The present data also testify to the frequency of recurrence, with a mean 17.9 endoscopies per patient.

To our knowledge, this is one of the first studies reporting a significant correlation between initial extension and progression in juvenile-onset RRP. The more levels initially involved, the greater the number of endoscopies performed. Three-level involvement emerged as a factor for great severity, with a 2-fold greater number of endoscopies. The impact of subglottic involvement on progression could not be shown to be significant, probably due to small sample size (subglottis, $n = 9$). There have been few studies on this question, but tracheal papillomatous lesions seem to be rarer,

Table 3
Multivariate analysis of risk factors.

Risk factors	n	Mean number of procedures	P	Recurrence at last assessment	P
Number of involved levels					
1	12	14.08	0.03	9	0.03
2	14	15.57		5	
3	6	30.67		1	
< 3 (combining 1 & 2)	26	14.88	0.01	14	0.18
3	6	30.67		1	
Subglottic extension					
Yes	9	23.67	0.16	2	0.12
No	23	15.56		13	
Bilateral involvement					
Yes	30	17.97	0.78	14	0.88
No	2	16		1	
Gender					
Female	19	19.95	0.4	8	0.72
Male	13	14.77		7	
Initial respiratory symptoms					
Yes	6	32.67	0.15	2	0.66
No	26	14.42		13	
Age (years)					
< 4	13	23	0.37	5	0.43
≥ 4	19	14.36		10	

Age did not significantly correlate with number of endoscopies ($P=0.17$, Pearson correlation). Significant differences in bold type.

although HPV DNA prevalence does not differ between trachea and larynx [8]. This may be due to lower frequency of HPV activation in the trachea; but subglottic and tracheal extensions incur a high risk of lower airway spread, where endoscopic treatment is limited.

The importance of bilateral involvement is mainly from the surgical point of view. Unilateral lesions have low risk of synechia or vocal-fold scarring and can often be treated in a single step; in bilateral lesions or lesions of the anterior commissure, on the other hand, 1-step surgery risks iatrogenic problems such as anterior commissure synechia [9]. Bilateral lesions often require multiple procedures or adjuvant treatment to avoid surgical complications. According to the American RRP Task-Force consensus, anterior or posterior commissure involvement is an indication for intralesional cidofovir injection [10]. As 30 of the present 32 patients had initial bilateral lesions, we were unable to analyze the impact of bilateral involvement on disease progression, although we still consider it to be a major factor guiding treatment.

Other known severity risk factors did not show significant impact in the present series. Young age at onset is said to be a critical factor for progression; notably, age 2–5 years, depending on the series, was associated with greater severity [11–20]. In the present series, under-4 year-olds underwent a greater number of endoscopies, but the difference was not significant ($P=0.37$), probably due to lack of power. HPV-11 genotype is also known to be associated with the most severe forms, with more recurrence and a greater number of endoscopies [12,14,20–22]. The present series failed to confirm this severity risk factor, due to incomplete HPV serotype data. Surgical technique may also affect progression. The present series used either laser or microdebrider (or both, over the duration of treatment), with laser phased out over the years. Most patients first treated by laser were later treated by microdebrider; only 4 were treated only by laser. This precluded analysis of the efficacy of the two techniques. When adjuvant treatment was required, intra-lesion cidofovir was the main option. Following US Task-Force guidelines, cidofovir was used in recurrent disease or anterior commissure involvement, which biased analysis of efficacy.

Based on our own observations and the data in the literature, we offer here a shortened assessment system for RRP laryngeal extension on first endoscopy, comprising 3 elements: (1) number of laryngeal levels involved, (2) subglottic or tracheal extension, (3) and uni- or bi-lateral involvement (Table 4).

Table 4
Short assessment system in first endoscopy in juvenile-onset RRP.

Number of laryngeal levels involved (subglottis, glottis, supraglottis)	
<input type="checkbox"/>	1
<input type="checkbox"/>	2
<input type="checkbox"/>	3
Subglottic or tracheal extension	
<input type="checkbox"/>	Yes
<input type="checkbox"/>	No
Uni- or bi-lateral involvement	
<input type="checkbox"/>	Unilateral lesion(s)
<input type="checkbox"/>	Bilateral lesions and/or anterior commissure involvement

There are few systems for assessment of the anatomic extension of RRP in the literature. The first was published by Kashima et al. in 1985 [23]. Derkay's classification followed in 1998 and is now the most widely used [3]. It attributes an anatomic score by summing the number and size of RRP lesions. Of the 25 sites, 13 are laryngeal: the 2 epiglottic surfaces, the 2 aryepiglottic folds, the 2 ventricular bands, the 2 vocal folds, the 2 arytenoid cartilages, the anterior and posterior commissures, and the subglottis. Each site is scored 0 to 3: 0 for no lesion, 1 for surface lesion, 2 for raised lesion, and 3 for bulky lesion; thus the maximum score is 39, for the larynx alone. The other sites are in the trachea, upper airway, esophagus, etc. This painstaking assessment has prognostic value: Derkay et al. [4], in a series of 17 patients, reported that each 1-point increase in total anatomic score reduced the interval between surgeries by 4 days; scores of 20 or more reduced the interval by 120 days. The Derkay scale has several advantages. It enables progression to be monitored, notably by means of diagrams and score charts. The score can guide decision-making for adjuvant treatment when there is no improvement over time or inter-procedure intervals begin to shrink, although this point has not been validated in the literature. The Derkay system has been implemented in certain studies. In a literature review of severity risk factors in juvenile-onset RRP, most of the 25 studies used the number of endoscopies as a marker of severity, and only 4 used the Derkay scale [2]. Wiatrak et al. reported higher Derkay scores in patients with tracheotomy, adjuvant treatment, caesarean delivery or Medicaid insurance [20]. Seedat et al. reported a trend for higher Derkay scores in HPV-11 than HPV-6 infection, although the difference was not significant: 27.4 vs. 19.2 ($P=0.08$) [22]. Carvalho et al.

reported non-significantly higher Derkay scores in juvenile than adult RRP: 5.5 vs. 3.1 ($P > 0.05$) [14]. Leung et al. found no significant correlation between socioeconomic status and Derkay score [16].

The 25-site Derkay scale is precise, but provides no immediately understandable information on laryngeal lesion location. We propose adding the short first-endoscopy assessment system described above. It can also be used independently in retrospective studies, whereas the Derkay classification is not adapted to retrospective inclusion.

5. Conclusion

In a large series of juvenile-onset RRP, initial extension of papillomatous lesions to multiple laryngeal levels or the subglottis was shown to be a severity risk factor, with greater number of endoscopies. We provide a succinct, immediately comprehensible assessment system in complement to the Derkay classification. This assessment is clinically, surgically and diagnostically relevant.

From our own experience, we recommend close follow-up of patients with subglottic or 3-level lesions. Further prospective studies will be needed, to determine new decision-trees according to the 3 severity risk factors known at first endoscopy: patient age; HPV serotype, and anatomic extension.

Study centers

Service d'ORL Pédiatrique et Chirurgie Cervico-Faciale, Hôpital d'Enfants de La Timone, Aix-Marseille Université, Marseille, France: Eric Moreddu, Jean-Michel Triglia, Richard Nicollas.

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Disclosure of Interest

The authors declare that they have no competing interest.

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