Clinical evaluation of pediatric patients with recurrent respiratory papillomatosis.

A longitudinal study at a Saudi Arabian tertiary care center

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ABSTRACT

Objectives: To study the clinical evaluation of recurrent respiratory papillomatosis (RRP) patients and the factors associated with the improvement in the Derkay's score as a measure of disease severity.

Methods: A retrospective cohort that included all juvenile RRP patients who were admitted to King Abdulaziz University Hospital, Riyadh, Saudi Arabia, between September 2015 and June 2022 and underwent surgical debulking.

Results: A total of 16 patients were eligible to join our study. Among them, 7 patients were males. Hoarseness of voice was the most frequent symptom. The median period of the follow-up was 56 months. Complete remission was achieved in 31.3%. The univariate linear regression model revealed that the cidofovir-treated patients had a significant reduction in the change value of Derkay's score compared to those without treatment (regression coefficient= -5.83, 95% confidence interval [CI]: [-11.5 to -0.143], p=0.045). Also, the increased first Derkay's score decreased the change value and subsequently increased the improvement chance of the disease (regression coefficient= -0.424, 95% CI: [-0.764 to -0.083], p=0.018). However, in the multivariate regression model, both variables showed non-significant results.

Conclusion: cidofovir treatment and higher Derkay's scores affected the disease improvement.

Keywords: recurrent respiratory papillomatosis, debulking, cidofovir, avastin

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Recurrent respiratory papillomatosis (RRP) is a rare chronic disease that affects the respiratory system. Per each 100,000 children and adults, there were 4.3 of children and 1.8 of adult were affected In United States.[1]

Juvenile-onset and adult-onset RRP are the 2 different forms of the disease. Juvenile-onset type is the more common and typically affects children under the age of 12.[2]

It is caused by human papilloma virus (HPV), which leads to exophytic epithelial lesions in the airways.[3] Human papilloma virus-6 and -11 have been reported to be the most common types, while HPV-11 has the most severe clinical course and is usually seen in the juvenile type. However, RRP has also occasionally contained HPV types 16, 18, 31, and 33.[3]

The clinical presentation of RRP can vary widely, depending on the location and extent of the papillomas.[4] The most common symptoms include hoarseness, difficulty breathing, coughing, and stridor.[4] In severe cases, RRP can lead to life-threatening respiratory obstruction.[4] Usually, RRP presents as a benign condition, but medical professionals have detected some cases of malignancy transformation.[3] Less than 1% of RRP cases develop into malignancies, and these cases are typically in adults who also have other factors like smoking or radiation exposure; however, they can also occur in children with extensive, prolonged, and distal spread.[3] Some individuals have spontaneous remission, while others have a chronic illness that lasts their entire lives.[1]

The diagnosis of RRP is carried out based on clinical presentation, imaging studies, and biopsy.[2] Tumor location and extent can be determined by using imaging studies including computed tomography and magnetic resonance imaging.[2] In order to verify the diagnosis and rule out cancer, a biopsy is required.[2]

Prevention of RRP can be achieved by vaccination. According to a review carried out by Benedict et al,[5] the incidence of RRP has been decreasing since the HPV vaccine was introduced. The administration of a single dose of gardasil in developing countries has been found to provide long-lasting immunity for at least 7 years.[1] The HPV vaccine could be a useful adjuvant treatment for RRP as the addition of HPV vaccination was linked to a longer interval between surgeries and a decline in the necessity of many operations.[6]

There is no available treatment for the cure; hence, therapy for these patients focuses on preserving voice quality and airway patency.[1] The treatment of RRP is primarily surgical.[2] The surgical management of RRP

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involves removing these papillomas using techniques such as microdebrider, laser surgery, or cold knife excision.[7] However, the anesthetic management during the endoscopic intervention of RRP can be challenging due to the location of the tumors and the potential for airway obstruction.[8]

The recurrence rate of RRP after surgical management varies depending on several factors, like age at the onset, disease severity, and the HPV subtype.[9] To reduce the risk of recurrence after surgery, adjuvant therapies such as antiviral medications (cidofovir), bevacizumab, or immunomodulatory agents may be used.[8]

In this study, we reported our experience in managing these challenging cases. The clinical outcomes and the possible affecting factors were investigated.

Methods. We carried out a retrospective study including all juvenile RRP patients who were referred and admitted to King Abdulaziz University Hospital, Riyadh, Saudi Arabia, between September 2015 and June 2022 and underwent surgical debulking. The patients were followed until January 2023 to determine whether their clinical outcome was complete remission, partial remission, or persistent disease. Ethical approval was acquired from the institutional review board at King Saud University, Riyadh, Saudi Arabia (E-22-7230), and the study was carried out according to principles of Helsinki Declaration. The inclusion criteria were juvenile RRP patients who were surgically treated in our center, had complete data, and had a follow-up of at least 6 months after the last intervention. We excluded adult patients, those with the missing last Derkay score as we could not determine their clinical outcome improvement, and patients with follow-up periods of less than 6 months.

High Derkay scores meant an increased severity of the diseases, while zero was given when there was no lesion, one in the case of a surface lesion, 2 in the raised lesion, and 3 in a bulk lesion. Then, these scores were summed to obtain a final score.[1]

We determined whether the clinical outcome was complete remission, partial remission, or persistent disease according to the improvement in the Derkay score. Persistent disease was defined as having the same score or a reduction of the initial score of less than 50%. Partial remission was determined if the reduction in the initial Derkay score was more than 50% but more than a score of 3, while complete remission was achieved if the Derkay score was 3 or less.

We reviewed the patients' medical records, including their baseline data, such as gender, age at diagnosis, length of follow-up, and clinical data, such as total number of debulking procedures, presenting symptoms, histology specimen results, complications, first and last Derkay scores, mean treatment interval (MTI), which is the total number of procedures over the total number of follow-up in months, number of patients treated with cidofovir, number of patients treated with avastin, and clinical outcome.

Statistical analysis. We carried out the analysis using Jamovi 2.3 software. We investigated the distribution of the data using the Shapiro-Wilk test for normality, which revealed that our data were not normally distributed. Therefore, the quantitative data were represented by median and (the first quartile value - the third quartile value), while the qualitative data were represented by number and frequency. First, the individual data of the included patients were described, followed by the baseline data. Univariate linear regression was carried out to investigate the factors associated with the change in the Derkay score. Then, multivariate linear regression was carried out to confirm the significant associations resulting from the univariate regression. The results were considered to be significant when p-values were <0.05.

Results. A total of 16 patients were eligible to join our study. Among them, 7 patients were males and 9 were females. Hoarseness of voice was the most frequent presenting symptom between the included patients. The median period of the follow-up was 56 months. Table 1 presents the individual data, while Table 2 shows all baseline data of the entire cohort.

We carried out univariate linear regression to investigate the associated factors and found that the first Derkay score and patients treated with cidofovir significantly affected the change in the Derkay score. The cidofovir-treated patients showed a significant decrease in the change value of Derkay score compared to those without treatment (regression coefficient [r]= -5.83, 95% confidence interval [CI]: [-11.5 to -0.143], p=0.045). Also, the increased first Derkay score decreased the change value and subsequently increased the improvement of the disease (r= -0.424, 95% CI: [-0.764 to -0.083], p=0.018). In the multivariate regression model, both variables showed non-significant results (Table 3).

On the other hand, other factors, such as gender (p=0.404), length of follow-up (p=0.254), specimen histology (p=0.774), MTI (p=0.496), treatment with avastin (p=0.685), and number of surgical procedures (p=0.476), did not have any significant association (Table 3).

Table 1 - Individual data of the included patients.

ID	Gender	Age at diagnosis (years)	Anatomical location of disease	Symptoms at initial presentation	Symptoms at the last clinic visit	Length of follow-up (months)	Total number of procedures	Number of Cidofovir sessions	Number of Avastin sessions	Clinical outcomes
1	F	4	Ant. commissure, Lt. VC	Aphonia, choking, cough, dyspnea on exertion	Hoarseness, noisy breathing on exertion	12	4	3	0	Partial
2	F	11	Ant. commissure, Lt. arytenoid, Rt. and Lt. VC, Lt. false VC, subglottic, trachea posterior wall	Hoarseness, noisy breathing, dyspnea on exertion	Noisy breathing	159	26	12	2	Partial
3	F	2	Rt. aryepiglottic fold, Lt. arytenoid, Rt. false VC	Hoarseness, biphasic stridor, dyspnea on exertion	Hoarseness, and noisy breathing on exertion	90	6	5	0	Complete
4	F	4	Laryngeal surface of epiglottis, Rt. and Lt. VC, Rt. and Lt. false VC, ant. commissure	Hoarseness, noisy breathing during sleep and exertion	Hoarseness and cough	13	6	5	0	Persistent
5	M	9	Ant. commissure, post-commissure, Rt. and Lt. VC, false VC, subglottic, post-nasopharyngeal wall, Rt. lateral nasopharyngeal wall, Lt. MT and nasal septum	Hoarseness, dysphagia, and stridor	Hoarseness	7	5	4	5	Persistent
6	M	3	Ant. commissure, Rt. and Lt. VC, Rt. and Lt. false VC	Hoarseness, noisy breathing on exertion	Hoarseness	30	16	4	11	Partial
7	M	3	Lt. VC	Hoarseness, aphonia, dyspnea, noisy breathing	Cough	58	15	5	8	Complete
8	F	1	Ant. commissure, Lt. VC, Lt. false VC	Hoarseness, weak voice	Hoarseness	123	17	3	8	Partial
9	M	0.92	Rt. VC, uvula	Hoarseness, weak cry, cyanosis, noisy breathing	Asymptomatic	64	13	4	6	Complete
10	M	2	Rt. VC	Hoarseness, dyspnea, stridor	Asymptomatic	72	2	0	0	Complete
11	M	1.25	Rt. pyriform, Rt. arytenoid, Rt. VC, uvula	Hoarseness, dyspnea, cyanosis	Asymptomatic	54	10	5	4	Complete
12	M	10	Lt. VC, Rt. and Lt. false VC	Hoarseness, noisy breathing, apnea during sleep	Hoarseness	6	3	0	3	Partial
13	F	3	Rt. and Lt. VC, ant. commissure, Rt. and Lt. arytenoid, interarytenoid	Hoarseness, noisy breathing	Hoarseness	39	9	0	5	Persistent
14	F	1.1	Laryngeal surface of epiglottis, ant. commissure, Rt. ventricle, nasal vestibule	Hoarseness	Asymptomatic	144	6	5	0	Persistent
15	F	2.3	Ant. commissure, Rt. VC, Rt. and Lt. false VC	Aphonia	Asymptomatic	12	3	0	2	Partial
16	F	9	Ant. commissure, Rt. and Lt. VC, Lt. false VC, Rt. ventricle	Hoarseness, dyspnea	Asymptomatic	121	7	1	0	Partial

ID: identification, F: female, M: male, Ant.: anterior, VC: vocal cord, Rt.: right, Lt.: left, MT: middle turbinate

Discussion. Our retrospective series study included 16 juvenile-onset patients with a 56-month average follow-up period. We found that the increase of the first Derkay score and treatment with cidofovir were significantly associated with a decrease in the change value of the Derkay score and improved the clinical outcome; however, the multivariate regression model did not yield significant results for both variables. Additionally, factors such as gender, length of follow-up, specimen histology, MTI, treatment with avastin, and the number of surgical procedures did not show any significant association.

Table 2 - Baseline data of included patients (N=16).

Variables	n (%)
Gender	
Male	7 (43.8)
Female	9 (56.3)
Age at diagnosis (year)	3 (1.81-5.25)
Total number of procedures	6.5 (4.75-13.5)
Length of follow-up (month)	56 (12.8-97.8)
Histology of tissue specimen	
Squamous papilloma	11 (68.8)
Squamous papilloma with HPV	2 (12.5)
Squamous papilloma with HPV P16	2 (12.5)
Squamous papilloma, with HPV-6, and HPV-11	1 (6.3)
Complications	
Anterior commissure adhesion	1 (6.3)
Disseminated RRP (pulmonary)	1 (6.3)
Extralaryngeal spread	5 (31.2)
Nasal vestibule	1 (6.3)
Posterior pharyngeal wall	1 (6.3)
Trachea	1 (6.3)
Uvula	2 (12.5)
Posterior glottic stenosis	1 (6.3)
None	8 (50.0)
First Derkay score	17 (12-19.8)
MTI	0.215 (0.107-0.362)
Patients treated with cidofovir	12 (75.0)
Patients treated with avastin	10 (62.5)
Change in Derkay's score	-11 (-13.3, -8.5)
Clinical outcome	
Complete remission	5 (31.3)
Partial remission	7 (43.8)
Persistent disease	4 (25.0)

Values are presented as numbers and precentages (%) or median and interquartile range (IQR). HPV: human papilloma virus, RRP: recurrent respiratory papillomatosis, MTI: mean treatment intervals

Table 3 - Univariate and multivariate regression results of the association between the change in Derkay score and other variables.

Variables	Univariate regression			Multivariate regression		
	Regression coefficient	95% CI	*P*-values	Regression coefficient	95% CI	*P*-values
Gender (male)	-2.25	(-7.87, 3.36)	0.404	-	-	-
Age at diagnosis in years	-0.446	(-1.25, 0.358)	0.254	-	-	-
Length of follow-up in months	-0.007	(-0.06, 0.049)	0.774	-	-	-
Histology of specimen (squamous papilloma)						
Squamous papilloma and HPV	3.275	(-4.914, 11.46)	0.401	-	-	-
Squamous papilloma and HPV P16	7.773	(-0.414, 15.96)	0.061	-	-	-
Squamous papilloma, HPV-6, and HPV-11	0.273	(-10.85, 11.4)	0.958	-	-	-
Complication						
Extra-laryngeal spread	-1.88	(-8.44, 4.69)	0.542	-	-	-
Posterior glottic stenosis	-5.87	(-18.08, 6.33)	0.312	-	-	-
Anterior commissure adhesion	-3.88	(-16.08, 8.33)	0.499	-	-	-
Disseminated RRP (pulmonary)	-8.88	(-21.08, 3.33)	0.138	-	-	-
First Derkay score	-0.424	(-0.764, -0.083)	0.018	-0.337	(-0.683, 0.009)	0.056
MTI	-4.52	(-18.4, 9.32)	0.496	-	-	-
Patients treated with cidofovir (non treated)	-5.83	(-11.5, -0.143)	0.045	-4.008	(-9.48, 1.46)	0.138
Patients treated with avastin (not treated)	-1.13	(-7, 4.73)	0.685	-	-	-
Total number of procedures	-0.151	(-0.592, 0.29)	0.476	-	-	-

CI: confidence interval, HPV: human papilloma virus, RRP: recurrent respiratory papillomatosis, MTI: mean treatment intervals

Hoesli et al[10] studied the safety of cidofovir as an adjuvant therapy of RRP. They found that the application of intra-lesional cidofovir in a significant number of patients with RRP did not result in any significant adverse effects and the risk of carcinoma or dysplasia was not raised by this treatment.

However, its efficacy was controversial in the literature.[11] McMurray et al[12] studied the efficacy of cidofovir in the management of aggressive form of RRP and reported a significant improvementin the Derkay Score after 12 months in both groups taking cidofovir and placebo. Also, Wierzbicka et al[13] reported that of the 32 patients having RRP, 18 experienced complete remission, and 13 demonstrated remission in lieu of cidofovir injection. Just one patient did not respond to the medication, and 4 others experienced changes to their injection sites. However, there were some hepatic toxic side effects which affected 2 patients. They concluded that treating laryngeal papillomatosis with intra-lesional cidofovir injection was a safe and successful option that ought to be taken into account for individuals who suffer a relapse of the condition.

Systemic avastin has proven its efficacy in the improvement of clinical outcomes and reducing recurrence in RRP patients as anti-vascular endothelial growth factor (VEGF) targeted therapy antagonizing the increased expression of VEGF on affected tissues of RRP patients.[14,15] In addition, systemic anti-VEGF targeted therapy showed efficacy in advanced cases such as elevated serum VEGF levels, robust tissue receptor expression, tracheobronchial involvement, and a high Derkay's score.[15]

In contrast to the promising efficacy of systemic injections, our study included only intra-lesion injections and showed no association between patients treated with avastin and the degree of clinical improvement. Intra-lesional cidofovir was associated with improvement in the clinical outcome with a controversy regarding its efficacy in the literature as specified previously.[11-13] Therefore, large randomized clinical controlled trials are needed to solve the controversy.

Study strengths & limitations. This retrospective study could enhance the quality of life of children patients with RRP as we found that treatment with cidofovir was associated with larger improvement in clinical outcomes.

On the other hand, our results were limited by the inherent bias of retrospective review and the low sample size, which was based only on patients who were referred to our center with complete data.

In conclusion, for patients who underwent debulking procedures, the initial Derkay score and the use of cidofovir had a significant impact on the change in the Derkay score. Patients who received cidofovir experienced a greater clinical improvement compared to others. However, a multivariate regression model did not show any significant results for these variables.

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