Clinical characteristics and HPV type in recurrent respiratory papillomatosis in Colombia

Gustavo Cuello, MD,[1,2] Gloria I Sánchez, MSc, PhD,[3] Roberto Jaramillo, MD,[1] Katherine Quintero, MD,[3] Armando Baena, MSc,[3] Adriana O'Byrne, MD,[1] Antonio J Reyes, MD,[1] Consuelo Santamaría, MD,[1] Julio C Reina, MD,[1,4] Nubia Muñoz, MD, MPH.[5]

Cuello G, Sánchez GI, Jaramillo R, Quintero K, Baena A, O'Byrne A, Reyes AJ, Santamaría C, Reina JC, Muñoz N. Clinical characteristics and HPV type in recurrent respiratory papillomatosis in Colombia. Salud Publica Mex 2013;55:416-420.

Abstract

Objective. Describe factors associated with aggressive forms of recurrent respiratory papillomatosis (RRP). **Materials and methods**. One hundred eighty-nine RRP cases diagnosed between 1985 and 2009 were identified in pathological records. HPV was detected by the SPF-10 method with broad spectrum primers, (version 1). **Results**. 113 patients had only one surgery (less aggressive) and 76, two or more interventions (more aggressive). The likelihood of aggressive lesions decreased with increasing age at diagnosis and HPV-11 was associated with no significant increase in the risk of aggressiveness. **Conclusions**. The age at diagnosis was the main determinant of RRP aggressiveness.

Keywords: recurrent respiratory papillomatosis; Papillomavirus infections; Papillomavirus vaccines; juvenile laryngeal papilloma; laryngeal neoplasms; Colombia

Cuello G, Sánchez GI, Jaramillo R, Quintero K, Baena A, O'Byrne A, Reyes AJ, Santamaría C, Reina JC, Muñoz N. Características clínicas y genotipo de VPH en papilomatosis respiratoria recurrente en Colombia. Salud Publica Mex 2013;55:416-420.

Resumen

Objetivo. Describir factores asociados con formas agresivas de papilomatosis respiratoria recurrente (PRR). **Material y métodos**. Se identificaron 189 casos de PRR diagnosticados entre 1985-2009 en registros patológicos. VPH fue detectado por el método SPF-10 con cebadores de amplio espectro, (versión 1). **Resultados**. 113 casos presentaron una intervención quirúrgica (menos agresivas) y 76, dos o más intervenciones (más agresivas). La probabilidad de lesiones agresivas disminuyó con el aumento de la edad al momento del diagnóstico y el VPH-11 se asoció con aumento no significativo del riesgo de agresividad. **Conclusiones**. La edad al momento del diagnóstico fue el principal determinante de la agresividad de PRR.

Palabras clave: papilomatosis respiratoria recurrente; infecciones por *Papillomavirus*; vacunas contra *Papillomavirus*; papiloma laríngeo juvenil; neoplasias laríngeas; Colombia

(1) Centro Médico Imbanaco. Cali, Colombia.
(2) Departmento de Otorrinolaringología, Facultad de Medicina, Universidad del Valle. Cali, Colombia.
(3) Grupo Infección y Cáncer, Facultad de Medicina, Universidad de Antioquia. Medellín, Colombia.
(4) Departmento de Pediatría, Facultad de Medicina, Universidad del Valle. Cali, Colombia.
(5) Instituto Nacional de Cancerología. Bogotá, Colombia.

Received on: November 26, 2012 • **Accepted on:** April 1, 2013
Corresponding author: Dra. Gloria Inés Sánchez, Cra 51D No. 62-29 Lab 283. Facultad de Medicina,Universidad de Antioquia. Medellín, Colombia.
E-mail: sanchezg@une.net.co

Recurrent respiratory papillomatosis (RRP) is a benign neoplasm primarily located in the larynx that can also affect the trachea and the lungs. Human Papillomavirus (HPV) 6 and 11 are the cause of these lesions. In children is called Juvenile-onset RRP (JORRP) and occurs before 12 years of age, with a peak between 1 and 4 years. Adult-onset RRP (AORRP) occurs mainly between 20 and 40 years of age. Although histologically benign, RRP is a devastating disease; some patients require more than four surgeries and treatments per year.[1,2] Studies exploring the relationship between clinical course and HPV type have not shown conclusive results.[3-11] We recently described the clinical characteristics of 189 RRP cases diagnosed between 1985 and 2009, identified in the records of pathology laboratories of three clinical centers of two Colombian cities (Cali and Medellin).[12] The mean age/SD at diagnosis of these cases was 31.5/23.5 years (range: <1-77 years). Fifty-eight cases (36.7%) were juvenile (<16 years old) and 100 (63.3%) were adult (>17 years old) cases. The majority of cases (115/189, 60.8%) were males, especially in adult cases (*p* value $\chi^2 = 0.04$). HPV testing could be conducted in 69% of cases (129/189). Among these, 95% were HPV positive; HPV 6, 11, and 16 contributed to 69, 27.1, and 7.8% of HPV positive cases respectively. This article reports a survey conducted in the records of all the study clinics covering full-length study period to describe the factors associated with the aggressiveness of RRP. In addition, 57 patient's mothers or patients themselves (whose contact details were in the clinical records) were interviewed with a standard questionnaire that collected information on residence, place of birth, history of sexually transmitted diseases of the mother, type of birth (vaginal or cesarean), number of surgeries for laryngeal papillomas, time between interventions, age of first sexual intercourse, oral sex and the frequency and presence of cold sores in life. For patients under 17 years of age their mothers were interviewed. Seventy-two patients could not be traced because of change of address.

This study was approved by the bioethics committee of the University Research Office at the University of Antioquia and the medical centers in Cali and Medellin. We found that 113 (59.8%) cases were less aggressive (only one surgical intervention) and 76 (40.2%) more aggressive (two or more surgical interventions). The probabilities of a more aggressive clinical course in relation to demographic variables and HPV type were estimated using unconditional logistic regression.

Table I shows that patients with more aggressive lesions were diagnosed at younger age than patients with less aggressive lesions (mean age at diagnosis/SD: 22.8/22.9 vs. 37.4/22.1; p< 0.001). Even further, there was a statistically significant lower likelihood of aggressive lesions with increasing age at diagnosis (table I). We also found that RRP cases over 12 years of age tend to be more aggressive in males than in females, but this difference was not statistically significant. The association between HPV type and degree of aggressiveness was evaluated among the 123 HPV positive cases.

Table II shows that RRP cases positive for HPV 11, and in particular those over 12 years of age, tend to be more aggressive after adjustment for age, but the increased risk was not statistically significant. Among cases with additional information obtained by telephone interview; very few reported a history of genital infections, only two patients' mothers reported a history of genital warts. Only three patients' mothers reported that their children were born after cesarean delivery. Twenty three of 32 patients reported a history of oral sex. In 17 of the 76 cases classified as more aggressive, the HPV type was detected in the biopsies taken during two or more surgical interventions.

Table III shows that the same viral type was detected in most follow-up visits; in only one case (Case No. 87) HPV 16 was detected in the first visit and HPV 11 in the second surgical intervention performed one month after the first. In conclusion, this retrospective study covering a 25 year period (1985-2009) shows that cases occurring before four years of age were more aggressive than those occurring later and HPV type was not the main determinant of a more aggressive clinical behavior. The majority of studies have reported that HPV 11-positive cases have a more aggressive behavior than HPV 6-positive cases;5,10,11 others have reported the contrary3,13 or no association.6,7 A study that included 118 JORRP cases with at least one year of follow-up and positive for only a single HPV type8 found that a more aggressive clinical course was more closely associated with early age at diagnosis than with HPV type. HPV 11 was more closely associated with early age at diagnosis, than it was associated with a more aggressive clinical course. These results are in agreement with our observations. An association between age at diagnosis and aggressive clinical behavior has also been reported from the National registry of RRP in the USA,14 and a Danish study.15 The transmission of HPV 6 or HPV 11 in JORRP most likely occurs from mother to child when the fetus is passing through an infected birth canal.16 The manner of transmission in AORRP is not known but evidence indicates that it may be associated with oral-genital contact.2 It was notable that 23 of 32 (72%) patients with AORRP reported a history of oral sex. Considering that this disease is rare, the main strengths of our study are its relative large sample size, long period covered (25 years), use of a standard protocol for lesion

Table I

Bivariate analysis of demographic characteristics of recurrent respiratory papillomatosis cases of clinical centers of Cali and Medellin, Colombia, 1985-2009

Characteristics	Total		More aggressive RRP		Less aggressive RRP		OR (95% CI)	p value*
	n	%	n	%	n	%		
Total	189	100.0	76	40.2	113	59.8		
Age y (mean/SD)	(31.5/23.5)		(22.8/22.9)		(37.4/22.1)			< 0.001‡
≤ 4	30	19.0	23	76.7	7	23.3	1	
5-12	27	17.1	13	48.1	14	51.9	0.28 (0.09-0.88)	
13-34	23	14.6	3	13.0	20	87.0	0.05 (0.01-0.20)	< 0.001
35-49	37	23.4	16	43.2	21	56.8	0.23 (0.08-0.67)	
≥ 50	41	25.9	9	22.0	32	78.0	0.09 (0.03-0.26)	
Missing information	31		12		19			
Trend *p*-value							< 0.001	
Gender								
Female	74	39.2	28	37.8	46	62.2	1	0.692
Male	115	60.8	48	41.7	67	58.3	1.17§ (0.54-2.52)	
Missing information	0		0		0			
Gender (≤12 years old) n=57								
Female	27	47.4	17	63.0	10	37.0	1	0.370
Male	30	52.6	19	63.3	11	36.7	0.57§ (0.16-2.01)	
Gender (≥13 years old) n=101								
Female	33	32.7	6	18.2	27	81.8	1	0.210
Male	68	67.3	22	32.4	46	67.6	1.93§ (0.67-5.54)	

* Deviance test
‡ Mann-Whitney test
§ Adjusted by age

microdisection and very sensitive PCR-based assay for HPV identification. Bias in the selection of cases and classification of outcome cannot be excluded. Unfortunately, information such as time elapsed between surgeries and size of the lesions was not possible to obtain in order to overcome this limitation. Nevertheless, this is to our knowledge the most complete series of cases in any Latin American country trying to elucidate the factors associated with the clinical course of PRR.

Acknowledgements

This research was supported in part by the University of Antioquia (Sustainability Strategy 2011-2012, CPT-1107) and in part by Merck &Co., Inc. (IISP HPV Proposal # 34). The authors express gratitude to Jehidys Montiel (microbiologist and bionalist) for genotyping of HPV. KQ was the beneficiary of the program young researchers from the University of Antioquia.

Declaration of conflict of interest: Nubia Muñoz has received fees for lecturing and honoraria for consulting advice from Merck & Company and Sanofi Pasteur MSD. Julio César Reina has been supported by grants and funding from Merck & Company through its institution for studies of HPV vaccines. Gloria Inés Sánchez has been supported by Merck & Company to attend conferences. The study was designed by Drs. Sánchez, Muñoz and Cuello and Merck & Co. has no role in study design, conduct, collection, analysis and interpretation of data or preparation of the manuscript.

Table II
Bivariate analysis of Human Papillomavirus genotypes and recurrent respiratory papillomatosis cases diagnosed in centers of Cali and Medellin, Colombia, 1985-2009

HPV type	*Total**		*More aggressive RRP*		*Less aggressive RRP*		*OR‡ (95% CI)*	*P§*
	n	*(%)*	*n*	*(%)*	*n*	*(%)*		
Total	123	(100.0)	49	(39.8)	74	(60.2)		
HPV 6 (all ages)								
Negative	34	(27.6)	13	(38.2)	21	(61.8)	1	0.738
Positive	89	(72.4)	36	(40.4)	53	(59.6)	1.34 (0.53-3.37)	
HPV 6 (≥13 years old at diagnosis, n = 69)								
Negative	18	(26.1)	5	(27.8)	13	(72.2)	1	0.895
Positive	51	(73.9)	15	(29.4)	36	(70.6)	1.13 (0.34-3.81)	
HPV-11 (all ages)								
Negative	88	(71.5)	34	(38.6)	54	(61.4)	1	0.482
Positive	35	(28.5)	15	(42.9)	20	(57.1)	1.45 (0.58-3.64)	
HPV 11 (≥13 years old at diagnosis, n = 69)								
Negative	51	(73.9)	13	(25.5)	38	(74.5)	1	0.290
Positive	18	(26.1)	7	(38.9)	11	(61.1)	2.04 (0.62-6.74)	
HPV-16 (all ages)								
Negative	113	(91.9)	45	(39.8)	68	(60.2)	1	0.839
Positive	10	(8.1)	4	(40.0)	6	(60.0)	0.96 (0.22-4.26)	
HPV 16 (≥13 years old at diagnosis, n = 69)								
Negative	63	(91.3)	18	(28.6)	45	(71.4)	1	0.808
Positive	6	(8.7)	2	(33.3)	4	(66.7)	0.92 (0.15-5.69)	

* Includes only HPV positive cases
‡ Adjusted by age
§ Deviance test

Table III

HPV DNA type during follow-up biopsies of individuals with more aggressive recurrent respiratory papillomatosis lesions of clinical centers of Cali and Medellin, Colombia, 1985-2009

Case No	*Surgical intervention number*	*Date of surgical intervention*	*HPV Type*
12	1	08/07/2005	6
	2	12/08/2005	6
	3	14/07/2006	6
54	1	27/04/2005	6
	2	25/11/2005	ND
57	1	24/02/1997	11
	2	12/09/2001	6,11
	3	29/04/2002	11
	4	11/04/2006	11
43	1	27/01/1999	6,16
	2	27/01/2000	6
83	1	11/03/1996	11
	2	02/06/1998	11,16
87	1	05/03/1998	16
	2	08/04/1998	11
90	1	29/08/1996	11
	2	23/12/1996	11
	3	01/04/1997	11
114	1	08/12/2006	6
	2	24/07/2007	6
	3	06/09/2007	6
119	1	11/03/2005	6
	2	18/07/2005	6,11
	3	19/10/2005	6
92	1	04/06/2004	6
	2	21/07/2005	6
139	1	03/12/2004	6
	2	15/12/2005	6
146	1	19/01/1995	6
	2	23/06/1995	6
	3	12/02/1998	6
155	1	23/04/2005	6
	2	25/10/2005	6
164	1	18/09/1997	6,11
	2	23/03/1999	11
171	1	17/06/2004	6
	2	10/02/2005	6
	3	30/06/2005	6
172	1	02/04/1998	6
	2	24/01/2000	6
174	1	30/01/2001	6,11,16
	2	15/09/2003	6,11

References

1. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008; 118:1236-1247.
2. Larson DA, Derkay CS. Epidemiology of recurrent respiratory papillomatosis. APMIS 2010; 118:450-454.
3. Padayachee A, Prescott CA. Relationship between the clinical course and HPV typing of recurrent laryngeal papillomatosis. The Red Cross War Memorial Children's Hospital experience 1982-1988. Int J Pediatr Otorhinolaryngol 1993; 26:141-147.
4. Pou AM, Rimell FL, Jordan JA, Shoemaker DL, Johnson JT, Barua P, *et al.* Adult respiratory papillomatosis: human papillomavirus type and viral coinfections as predictors of prognosis. Ann Otol Rhinol Laryngol 1995; 104:758-762.
5. Rimell FL, Shoemaker DL, Pou AM, Jordan JA, Post JC, Ehrlich GD. Pediatric respiratory papillomatosis: prognostic role of viral typing and cofactors. Laryngoscope 1997; 107:915-918.
6. Peñaloza-Plascencia M, Montoya-Fuentes H, Flores-Martinez SE, Fierro-Velasco FJ, Peñaloza-González JM, Sanchez-Corona J. Molecular identification of 7 human papillomavirus types in recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2000; 126:1119-1123.
7. Gabbott M, Cossart YE, Kan A, Konopka M, Chan R, Rose BR. Human papillomavirus and host variables as predictors of clinical course in patients with juvenile-onset recurrent respiratory papillomatosis. J Clin Microbiol 1997; 35:3098-3103.
8. Buchinsky FJ, Donfack J, Derkay CS, Choi SS, Conley SF, Myer CM, 3rd, *et al.* Age of child, more than HPV type, is associated with clinical course in recurrent respiratory papillomatosis. PLoS One 2008; 3:e2263.
9. Gerein V, Rastorguev E, Gerein J, Draf W, Schirren J. Incidence, age at onset, and potential reasons of malignant transformation in recurrent respiratory papillomatosis patients: 20 years experience. Otolaryngol Head Neck Surg 2005; 132:392-394.
10. Rabah R, Lancaster WD, Thomas R, Gregoire L. Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease. Pediatr Dev Pathol 2001; 4:68-72.
11. Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 2004; 114:1-23.
12. Sánchez GI, Jaramillo R, Cuello G, Quintero K, Baena A, O'Byrne A, *et al.* Human papillomavirus genotype detection in recurrent respiratory papillomatosis (RRP) in Colombia. Head Neck 2013; 35:229-234.
13. Mounts P, Kashima H. Association of human papillomavirus subtype and clinical course in respiratory papillomatosis. Laryngoscope 1984; 94:28-33.
14. Reeves WC, Ruparelia SS, Swanson KI, Derkay CS, Marcus A, Unger ER. National registry for juvenile-onset recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2003; 129:976-982.
15. Silverberg MJ, Thorsen P, Lindeberg H, Ahdieh-Grant L, Shah KV. Clinical course of recurrent respiratory papillomatosis in Danish children. Arch Otolaryngol Head Neck Surg 2004; 130:711-716.
16. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003; 101:645-652.