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# Clinical characteristics and HPV type in recurrent respiratory papillomatosis in Colombia

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## 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 I). **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

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## 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 I). **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

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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.<sup>1,2</sup> Studies exploring the relationship between clinical course and HPV type have not shown conclusive results.<sup>3-11</sup> 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 Medellín).<sup>12</sup> 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 Medellín. 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;<sup>5,10,11</sup> others have reported the contrary,<sup>3,13</sup> or no association.<sup>6,7</sup> A study that included 118 JORRP cases with at least one year of follow-up and positive for only a single HPV type<sup>8</sup> 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,<sup>14</sup> and a Danish study.<sup>15</sup> 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.<sup>16</sup> The manner of transmission in AORRP is not known but evidence indicates that it may be associated with oral-genital contact.<sup>2</sup> 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 <sup>‡</sup>
≤ 4	30	19.0	23	76.7	7	23.3	1	< 0.001
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)	
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 <sup>§</sup> (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 <sup>§</sup> (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 <sup>§</sup> (0.67-5.54)	

\* Deviance test

<sup>‡</sup> Mann-Whitney test

<sup>§</sup> Adjusted by age

microdissection 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.

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**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

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