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ORIGINAL ARTICLE

Anogenital lesions produced by Human Papillomavirus. Prevalence study in children and adolescent not vaccinated

Lesiones anogenitales por Virus Papiloma Humano. Estudio de prevalencia en niños, niñas y adolescentes no vacunados

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What do we know about the subject matter of this study?

Human papillomavirus (HPV) infection is a sexually transmitted infection in adults, with unknown prevalence in children and adolescents in Chile.

What does this study contribute to what is already known?

The prevalence of HPV infection in unvaccinated children is 30%. In adolescents, it is associated with sexual contact and high-risk HPV. Visual inspection of genital and perianal lesions does not allow us to determine the etiology, so it is necessary to perform a PCR test for HPV.

Abstract

In Chilean children and adolescents, human papillomavirus (HPV) infection prevalence is unknown. In 2014, the HPV vaccine was incorporated into the National Immunization Program for girls, and since 2019 for boys. **Objective:** To determine the prevalence, genotypes, and characteristics of HPV infection in children and adolescents with anogenital lesions not vaccinated against HPV. **Patients and Method:** Children and adolescents with anogenital lesions who consulted at the Luis Calvo Mackenna Children's Hospital between 2013 and 2017 were studied. The reason for consultation, age, sex, family history of HPV lesions, history of sexual abuse, and consensual sexual activity were recorded. HPV was detected by PCR and typification by reverse hybridization of the L1 gene. The samples were analyzed in the Oncogenic Virus Section of the Institute of Public Health. **Results:** 110 patients were studied; 44.5% were children. HPV was detected in 34 cases (30.9% [CI95% 22.4- 40.4]), 22 (44.9%)

Keywords:
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were children and 12 (19.7%) adolescents. Eleven (91.7%) adolescents had a history of sexual contact ($p < 0.005$); 4 (18.2%) children disclosed sexual abuse. HPV was found in 25% of patients with genital lesions and 50% with perianal lesions ($p < 0.015$). The most frequent genotypes were 59, 58, 16, 18, 6, and 11. Only low-risk genotypes were detected in children and high-risk genotypes were detected in 11/12 (91.7%) of HPV (+) adolescents. **Conclusion:** The prevalence of HPV infection was 30%. In adolescents, the infection was related to sexual contact and high-risk HPV. In children, it was associated with low-risk genotypes. Perianal lesions are more frequently associated with HPV infection than genital lesions in children and adolescents. The visual inspection does not allow to specify the etiology of the genital lesions, so it is necessary to perform a PCR test for HPV.

Introduction

Human Papillomavirus (HPV) is the most common sexually transmitted infection (STI) worldwide[1]. The prevalence of HPV infection in adolescent females aged between 14-19 years is 35%[2], and in those sexually active it can reach up to 82%[3]. In Chile, condyloma acuminata accounts for 30.9% of STIs, with the highest prevalence present in people under 25 years of age (41.7%)[4].

About 220 HPV genotypes have been identified and, according to their carcinogenic potential, they are classified into high and low oncogenic risk genotypes[5]. 75 to 90% of immunocompetent persons with external anogenital warts are infected by the low-risk HPVs genotypes 6 and 11[6]. High-risk HPVs genotypes 16 and 18 are also common in genital tract infection, accounting for two-thirds of cervical and vulvar cancers in women, and penile and anal cancers in men. In 2007, a multicenter study of HPV prevalence in Chile was carried out in adults consulting at STI centers and revealed a 32.6% prevalence of genotypes 6 and 16 and 20.3% of genotype 11[4].

The age of presentation of anogenital condylomas in children is 2.8 to 5.6 years on average[6]. In girls, they are located in the vulva, perianal region, periurethral, hymen, and vagina, and in boys mainly in the perianal region. The most common genotypes are HPV-6 and HPV-11[6]. In the pediatric age group, HPV infection is considered to be periconceptional by vertical transmission from mother to child, caregiver inoculation (person who changes diapers or bathes the child), autoinoculation, or by sexual violence[7]. HPV infections in children and adolescents can be difficult to diagnose clinically as they may present as nonspecific papules, genital mucosal micropapules, or verrucous papules, needing molecular testing to identify HPV[7,8].

In 2006, the tetravalent vaccine for HPV 6, 11, 16, and 18 genotypes was licensed by the Food and Drug Administration (FDA). Then, in the second half of 2014, it was included in the National Immunization Program (NIP) of our country, indicating two doses in girls aged 9 to 10 years, and in 2019, boys were included in the vaccination plan[9]. The effectiveness of the vaccine in reducing the detection of HPV-16 and 18 in cervical samples and prevention of genital condylomas caused by HPV-6 and 11 has been demonstrated in studies conducted in Australia[10]. However, there are still no data on the impact of vaccination in Chile.

The prevalence and distribution of HPV genotypes in children and adolescents are unknown in our country. The objective of this study was to determine the prevalence, genotypes, and characteristics of HPV infection in children and adolescents with anogenital lesions who were not vaccinated for HPV and who consulted pediatric gynecology and dermatology in a pediatric hospital.

Patients and Method

Cross-sectional study carried out from April 2013 to August 2017 which included 132 girls, boys, and adolescents who consulted at the pediatric gynecology and/or dermatology unitat the *Hospital Luis Calvo Mackenna*. Inclusion criteria were physical examination findings of anogenital cutaneous or mucosal lesions suggestive of HPV infection of the type nonspecific papules, micropapules, verrucous papules, cauliflower-like exophytic lesions of the genital mucosa; in females located in the vulva, vagina, or cervix (condyloma), and in males located in the penis, balanopreputial sulcus, or scrotum. Lesions in the anus and perianal area were also considered in both sexes. Exclusion criteria were having received the HPV vaccine.

The history of each patient was recorded on a specially designed form, including reason for consultation, age, sex, family history of HPV lesions, history of sexual violence in children and adolescents, and consensual sexual activity in adolescents. The history of sexual violence was obtained from the Family Courts or from professionals of the Child Protection Committee of the hospital, which performs a biopsychosocial evaluation of patients suspected of sexual violence.

The physical examination consisted of a general skin examination, evaluation of pubertal development, anogenital examination, description of the location, and appearance of the lesions to be studied.

Patients were classified into children and adolescents.

Sampling

A pediatric gynecologist performed the genital examination of girls and collected samples with a swab from each of the lesions suspected of HPV infection. A dermatologist collected anal lesions samples in girls and boys and genital lesions in boys.

The sample was obtained by rubbing the lesion with a swab, which was introduced into a sterile tube and immersed in a viral transport medium (Hank's balanced salt solution pH 7.2 with 7.5% bovine serum albumin). This medium is used as a transport preservative and antibacterial medium for gynecological specimens. The sample was kept at 4-25 ºC and sent to the laboratory of the Oncogenic Virus Section of the Viral Diseases Sub-Department of the Institute of Public Health (ISP) of Chile for molecular study.

Molecular study

HPV detection was performed by polymerase chain reaction (PCR) using the PGMY09/11 primer[11]. This technique amplified the types of HPV that affect the mucosa, producing a 450 bp amplicon of the HPV L1 gene. To confirm that the DNA was extracted in sufficient quantities and to rule out the presence of amplification inhibitors, partitions for a target cell and human leukocyte antigens (HLA) histocompatibility were included, producing a 230 bp amplicon. The amplicons were detected by agarose gel electrophoresis with GelRed staining and UV transillumination, registering the results by digitized photography. Samples with an amplified HPV band were considered suitable and were typed by reverse line blot (RLB) hybridization.

Samples without HPV and HLA bands could not be interpreted and were considered invalid or insufficient.

PCR reactions

PCR was performed with 5 µl of DNA in a 50 µl reaction solution containing 1.25 U of AmpliTaq Gold, 1X PCR buffer II, 0.2 mM dNTPs, 80 nM of each PGMY09 and HMB01 primer, 80 nM of each PGMY11 biotinylated primer, 20 - 40 nM of each HLAdQ primer and 3.0-1.5 mM $MgCl_2$. The amplification program consisted of an initial stage of 9 min at 95ºC, 45 cycles (30 sec at 95ºC, 90 sec at 55ºC, and 120 sec at 72ºC), and a final stage 5 min at 95ºC.

Afterward, electrophoresis was performed on 2% agarose gels in 1X TBE buffer, loading 10 µl of each sample. Additionally, 3-5 µl of the molecular weight markers were loaded to verify the size of the amplicons produced by the PCR technique.

HPV typing by reverse line blot (RLB) hybridization

HPV amplicons from PCR-positive samples were subsequently thermally denatured in a low-salt solution. Then, the biotinylated HPV amplicons were hybridized with probes specific to different HPV genotypes, which were covalently attached to a nylon membrane. After washing, the biotinylated amplicon-probe hybrids were revealed by chemiluminescence on autoradiographic film. This method is a reference technique supported by the World Health Organization HPV LabNet (WHO HPV LabNet)[12]. Using this method, the following 32 most prevalent high- and low-risk HPV genotypes can be simultaneously typed: 6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 69, 70, 73, 82, 83, and 84.

Definitions

Children: Tanner Scale Stage I.

Adolescents: Tanner Scale Stages II to V.

Relative HPV carrier: Person living with the patient who had a history of HPV skin or genital lesions.

Sexual violence: Includes different forms of sexual aggression such as sexual abuse, rape, sexual exploitation, exposure to pornography, and cyber harassment.

Sexual exploitation: A form of sexual abuse in which an adult involves children or adolescents in sexual activities in exchange for economic remuneration.

Invalid sample: Sample without bands for HPV or HLA histocompatibility.

HPV positive (+): Patient with HPV detected in the lesion studied.

HPV negative (-): Patient without HPV detected in the lesion studied.

Statistical Analysis

Data are presented as mean, median, interquartile range (IQR), standard deviation, and proportions. The chi-square test and the difference of proportions test were used to compare frequencies between groups. A p-value < 0.05 was considered significant. Analyses were performed with the STATA software.

Ethics

The project was approved by the Pediatric Scientific Ethics Committee of the Eastern Metropolitan Health Service (EMHS). Informed consent was requested from parents or guardians, and assent was requested from patients over 12 years of age.

Results

A total of 132 patients were studied; 22 cases were eliminated since 12 had an invalid sample, 9 did not meet the inclusion criteria, and one did not give consent. Valid HPV PCR results were obtained in 110 patients with anogenital lesions on physical examination, 49 (44.5%) were children, and 61 (55.5%) were adolescents.

HPV infection was detected in 34/110 patients (30.9% [95% CI 22.4-40.4]), where 22/49 (44.9%) were children and 12/61 (19.7%) were adolescents. The median and IQR age of HPV (+) children was 3.8 (2.75) years versus 6.8 (5.5) years for HPV (-) (p = 0.04); while in HPV (+) adolescents was 14.4 (1.8) years versus 13.1 (3.3) years for HPV (-) (p 0.18).

A family history of papillomavirus lesions was found in 10/22 (45.5%) HPV (+) children and 8/27 (29.6%) in HPV (-) cases (p 0.253). A history of sexual violence was found in 4/22 (18.2%) HPV (+) cases and 2/27 (7.4%) in HPV (-) cases (p 0.252).

In adolescents, 8/12 (66.7%) HPV (+) cases had history of sexual violence versus 5/49 (10.2%) HPV (-) cases (p < 0.005), and consensual sexual activity in 3/12 (25%) HPV (+) cases versus 1/49 (2%) of HPV (-) cases (p < s0.005) (Table 1).

In total, genital HPV (+) and HPV (-) lesions were observed in 72.7% (80/110) of patients, and anal HPV (+) and HPV (-) lesions in 29.1% (32/110) of patients. Of the total genital lesions (n = 80), 25% (20/80) were HPV (+) and of the total anal lesions (n = 32), 50% (16/32) were HPV (+), (p 0.015) (Table 2). Two patients had both genital and anal lesions.

When comparing the proportion of HPV(+) and (-) lesions according to lesion type and location, HPV (-) lesions presented 60.5% in genital nonspecific papules and the HPV (+) lesions presented 29.41%. There were no differences in genital lesions of the mucosal micropapules type. Regarding verrucous genital lesions, 44.12% were HPV (+) versus 17.1% HPV (-) (p: 0.002). In the anus and perianal region, verrucous lesions were 50.0% in HPV (+) compared with HPV (-) lesions with 18.75% (p < 0.062). There was no information to compare lesions of the cutaneous micropapules type and condylomas of the perianal area (Table 2).

Regarding genotypes, 19 HPV genotypes were detected. The most frequent were 59, 58, 16, 18, 6, and 11. In children only genotypes of low oncogenic risk were found (Figure 1). 12 adolescents were HPV (+): one had a single infection by low-risk genotype (HPV-6), 5 had a single infection by high-risk HPV, 3 had multiple infections by high- and low-risk genotypes, and 3 had multiple infections by high oncogenic risk genotypes. Of the infected adolescents, 91.7% had high-risk HPV (Table 3).

7 patients were infected by multiple genotypes: one girl and 6 adolescent carriers of high- and low-risk HPV, 4 of whom were victims of sexual violence, and one patient was immunosuppressed after liver and kidney transplantation (Table 4).

Discussion

The prevalence of HPV infection in unvaccinated children and adolescents who presented anogenital lesions on physical examination during consultation in Gynecology or Dermatology at the *Hospital de niños Luis Calvo Mackenna* was 30.9%. Of these, 44.9% were children and 19.7% were adolescents. Only HPV genotypes of low oncogenic risk were detected in children, while high-risk genotypes were found only in adolescents.

In our study, the percentage of children with HPV (+) anogenital lesions was very similar to what has been published[6], however, this does not occur in adolescents[13], which could be explained because the population studied was obtained in a pediatric hospital.s. The age of the HPV (+) children was lower than that found in the HPV (-) group, which, according to some authors, is related to vertical transmission during childbirth or infection by persons performing anogenital hygiene of the children[7]. About 50% of the children with HPV (+) lesions had history of an HPV carrier family member, without establishing a statistically significant difference in relation to those children with HPV (-) lesions.

Determining the HPV transmission route in pediatric patients is challenging and, although there are several routes of infection, it is important to define whether the infection occurred through sexual contact[8]. In this study, only 11 children infected with HPV were evaluated by collaborating organizations of the Family Courts and the Child Protection Committee of the hospital, finding in four of them history of sexual violence and two children with anamnestic history of sexual violence had HPV (-) anogenital lesions. Although there are few HPV (+) children with history of sexual violence, this has a great impact on the life of each child, because it allows interrupting the neurobiological damage caused by this type of abuse.

The prevalence of HPV in adolescents was lower than in other studies[4], which was concentrated in those who had had sexual contact, either through sexual violence or consensual sexual activity, which agrees with the published data on the relationship between HPV infection and initiation of sexual activity[14]. In children, only low-risk oncogenic HPV genotype was detected, the most frequent being HPV-6 and 11, in contrast to other studies that have reported high-risk HPV[15,16].

Table 1. Characteristics of patients with anogenital lesions infected vs. uninfected by Human Papilloma Virus

HPV detection	HPV (+)* N (%)	HPV (-)** N (%)	Total N (%)	*P*
Children	22 (44.9)	27 (55.1)	49 (44.5)	
Adolescents	12 (19.7)	49 (80.3)	61 (55.5)	0.004
Total	34 (30.9)	76 (69.1)	110 (100)	
Age (years)	Years median (IQR)	Years median (IQR)		
Children	3.8 (2.75)	6.8 (5.5)		0.042
Adolescents	14.4 (1.8)	13.1 (3.3)		0.183
Relatives HPV carrier	Cases n (%)	Cases n (%)		
Children	10/22 (45.5)	8/27 (29.6)	18/49 (36.7)	0.253
Adolescents	4 /12 (33.3)	8/49(16.3)	12/61 (19.7)	0.184
Sexual contact				
Children				
Sexual violence	4 /22(18.2)	2/27 (7.4)	6/49 (12.2)	0.252
Adolescents				
Sexual violence	8/12 (66.7)	5/49 (10.2)	13(21.3)	0.000
Sexual activity	3/12 (25.0)	1/49 (2.0)	4 (6.7)	0.004

*HPV (+) Human papilloma virus detected. **HPV (-) Human papilloma virus was not detected. ***IQR: Interquartile range.

Table 2. Type of anogenital lesions according to location in children and adolescents and detection of human papillomavirus infection

Appearance of the lesion	Total lesions			By Area			
	All areas n = 110*			Genital n = 80		Ano-perianal = 32	
	*HPV (+) n (%)	HPV (-) n (%)	p	*HPV (+) n (%)	HPV (-) n (%)	*HPV (+) n (%)	HPV (-) n (%)
Nonespecific papules	10 (29.41)	46 (60.5)	0.002*	6 (30.0)	37 (61.7)	4 (25.0)	9 (56.3)
Mucosal micropapules	5 (14.70)	13 (17.1)	0.753	5 (25.0)	13 (21.7)	0	0
Verrucous	15 (44.12)	13 (17.1)	0.002*	7 (35.0)	10 (16.7)	8 (50.0)	3 (18.75)
Cutaneous micropapules	3 (8.82)	1 (1.3)	0.052	1 (5)	0	2 (12.5)	1 (6.3)
Condylomatous mass	3 (8.82)	1 (1.3)	0.052	1 (5)	0	2 (12.5)	1 (6.3)
Fissure	0	2 (2.6)	-	0	0	0	2 (12.5)
Total	#34	76		#20	60	#16	16

Total patients with HPV lesions (+): 34 Total patients with HPV lesions (-) 76. Total patients with genital lesions: 80 Total patients with anal lesions: 32. *HPV (+) Papillomavirus detected. #: 2 patients present genital and anal lesions.

High-risk genotypes were found only in the group of sexually active adolescents, with genotypes 59, 58, 16, and 18 as the most frequent. This coincides with what was found in cervical cancer surveillance in Chile[17].

Perianal lesions were more frequently associated with HPV infection in children and adolescents than genital lesions. Visual inspection of genital lesions did not predict whether the etiology of these lesions was HPV. PCR is the test that allows determining whether the lesions are due to papillomavirus. Without this test, it would have been erroneously assumed that nonspecific papule-type lesions were caused by HPV and, on the other hand, HPV infection in micropapule-type

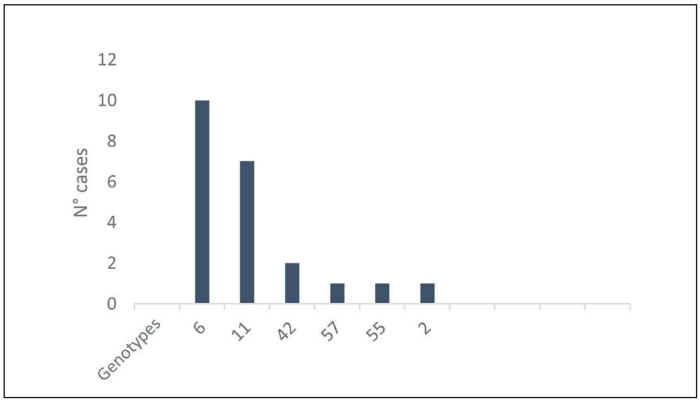

Figure 1. Frequency of low-risk Papillomavirus genotypes detected in children.

lesions of the genital mucosa would have gone unnoticed.

Infection by various HPV genotypes was found in 50% of infected adolescents, a figure much higher than in another study on university students[14]. This condition is associated with high-risk sexual behaviors, such as initiation of sexual activity at an early age, multiple partners, sexual violence, sexual exploitation, or immunosuppression. Multiple infections present a high risk of developing neoplastic lesions[18].

In our country, it is perhaps too early to draw conclusions on the impact of vaccination with the tetravalent vaccine. This vaccine does not protect against infection by the high-risk genotypes HPV-51, 52, and 58 detected in our study, which are present in the nonavalent vaccine, not yet incorporated in the NIP. Also, neither vaccine contains the HPV-59 genotype, the most frequent high-risk virus in this sample. The study was initiated before the incorporation of the HPV vaccine into the NIP. A review of the National Immunization Registry found that half of the adolescent patients included in the study who were HPV (+) and currently are over 18 years of age had not been immunized. As for the HPV (+) children, 23.5% have been vaccinated after the study[19].

In Decree 7 about Regulations Epidemiological Surveillance of Transmitted Diseases 2019, the Ministry of Health incorporated papillomavirus infection as sentinel notification[20]. This surveillance could not be implemented yet due to the epidemiological situation related to COVID-19 present these last two years.

Regarding vaccination coverage, it reached 89.2% in boys and 92% in girls in 4th and 5th grade in 2019, and in 2020 coverage dropped to 74.6% and 68.6%[21], probably secondary to the closure of schools due to the pandemic.

Among the limitations of the study is the reduction in the number of cases included due to invalid samples, possibly because the scraping of the lesion was insufficient. Another limitation is that the vertical transmission route could not be detected in children because many mothers have asymptomatic cervical infections[22]. In relation to HPV transmission through sexual contact, for various reasons, not all HPV (+) patients were referred to the Child Protection Committee and only 50% of them were evaluated; this data could be improved by evaluating 100% of infected children, which we hope to achieve in our clinical practice.

We consider the results of this study valuable as it provides insight into HPV infection and its characteristics in unvaccinated patients for papillomavirus attending a pediatric hospital. Although it is described that most children and adolescents have the immunological capacity to eradicate papillomavirus, it is interesting to know the genotypes that are involved in HPV infection in our children and adolescents since cases of low- and high-grade vulvar intraepithelial neoplasia have been reported at early ages[15,16,23,24]. These results

Table 3. Human papillomavirus genotypes of low and high oncogenic risk in adolescents

Papillomavirus		
Low risk genotypes	High risk genotypes	Number of cases
6		1
	57;59;18;16	5
6;11;42;53,84	16;34;51; 52:58;69;73	3
	16;18;31;39;51;58;59	3
Total		12

Table 4. Clinical characteristics of patients infected with multiple Human Papilloma Virus genotypes

Case	Age (years)	Genotypes	Background	Appearance of the lesion
1	3	6, 42	HIV positive mother. Genital wart carrier	Multiple perianal verrucous papules
2	14	56, 58, 59	Victim of sexual exploitation	Perineal verrucous papules
3	14	42, 51, 68	History of sexual violence. High risk behaviors	Verrucous papules on labia minora and introitus
4	13	51, 58, 59	Victimo f sexual exploitation	Mucosal micropapules on labia minora and cervix
5	16	6, 11, 42, 51, 59	Consensual sexual activity. Liver and kidney transplanted	Condylomatous mass of the vulva
6	14	16, 18, 31, 39, 58, 59	History of sexual violence. High risk behaviors	Micropapules in hy men
7	17	16, 34, 52, 53, 58, 59, 73, 84	Consensual sexual activity	Micropapules in labia minora

show that underage adolescents who have suffered sexual violence are unfortunately exposed to infection by multiple genotypes of high-risk papillomaviruses.

Conclusion

The prevalence of HPV infection in unvaccinated children and adolescents with anogenital lesions on physical examination was 30%. In adolescents who tested positive for HPV, a history of consensual sexual activity or sexual violence was found in two-thirds of the cases. The high-risk genotypes detected were concentrated in adolescents and at least three of these genotypes were found in the nonavalent vaccine. Multiple papillomavirus infections were observed in patients who were victims of severe sexual violence and in immunosuppressed patients.

It is necessary to perform a PCR test for papillomavirus since visual inspection does not allow us to determine the etiology of genital lesions.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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