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The Prevalence of Genital Human Papillomavirus Infections in Abused and Nonabused Preadolescent Girls

Catherine Stevens-Simon, MD*; Donna Nelligan, CHA, PA*; Paula Breese; Carole Jenny, MD§; and John M. Douglas, Jr, MD||

ABSTRACT. *Objective.* To compare the prevalence of genital human papillomavirus (HPV) infections in sexually abused and nonabused preadolescent girls and assess the feasibility of conducting a longitudinal study of the natural history of HPV infection in this population.

Method. Consecutively referred, 5- to 12-year-old girls who were evaluated for sexual abuse by a Child Advocacy and Protection Team were invited to participate in the study. During a standard forensic medical examination, 2 specimens for HPV testing were obtained (one by rubbing a Dacron swab over the perineum and the other by lavaging the vagina with phosphate-buffered saline). The specimens were evaluated for HPV DNA by polymerase chain reaction using MY09/11 consensus primers and high-risk (16,18,31,33,35,39,45,51,52,56,58) and low-risk (6,11,42,43,44) types were detected with a solution hybridization assay, the SHARP Signal System (Digene Diagnostics). The genital area was examined for warts and subclinical, colposcopic evidence of HPV. Participants were invited to return for longitudinal evaluation at 4-month intervals for 2 years.

Results. Sexual abuse was confirmed in 29 (72.5%) of the 40 study participants, suspected in 2 (5%), and ruled out in 9 (22.5%). None of the girls had genital warts or abnormal colposcopic findings. HPV DNA was detected in 5 (16%) of the 31 girls with confirmed or suspected sexual abuse (1 with high-risk and 4 with low-risk types) and none of the nonabused girls (Fisher's Exact test). Girls who tested positive and negative for HPV did not differ significantly in age or type of abuse. Despite close telephone follow-up and numerous attempts to schedule appointments, none of the participants returned for follow-up.

Conclusions. Genital HPV infection is more common among sexually abused than nonsexually abused girls, with the majority of infections not clinically apparent. Because it is so difficult to study the natural history of these infections in abused children, it may be necessary to draw inferences about the long-term sequelae of pediatric HPV infections from longitudinal studies of girls who voluntarily initiate sexual activity soon after

menarche. *Pediatrics* 2000;106:645-649; *human papillomavirus, sexual abuse, colposcopy.*

ABBREVIATIONS. HPV, human papillomavirus; SD, standard deviation; CAP, Child Advocacy and Protection Team; PCR, polymerase chain reaction.

The epidemiology and natural history of genital human papillomavirus (HPV) infection in children have not been well-defined. Studies in adults indicate that genital HPV infections are largely sexually transmitted.^{1,2} However, in children, the mode of transmission continues to be debated.²⁻¹⁶ In addition to the evidence supporting transmission during sexual abuse, children (particularly those <5 years old), may acquire genital HPV perinatally (from their infected mothers), and possibly by autoinoculation or heteroinoculation from nongenital cutaneous warts (during diapering or bathing), and by indirect means from contaminated fomites (such as towels).²⁻¹⁶ Clinically apparent genital warts are rare in children and studies designed to evaluate their source have produced estimates of sexual transmission ranging from 0 to nearly 100%.²⁻¹⁶ In the only study that directly compared the rate of virologically assessed genital HPV infection in sexually abused and nonabused children, the prevalence of HPV DNA was found to be significantly higher in the cases (33%) than the controls (0%) ($P = .015$).¹⁴ However, other investigators have reported that HPV DNA is detectable in <5% of abused children.¹⁶ Although neither study reported on the interval between sexual contact and diagnostic assessment, given the transient nature of most subclinical genital HPV infection,^{1,17-22} interval differences could account for this variability of the reported prevalence of genital HPV.

Pediatric HPV infections are concerning because epidemiologic studies in adolescents and adults and case reports in children strongly implicate certain high-risk HPV types in the etiology of dysplastic tissue abnormalities and anogenital cancers.^{1,2,17-27} The natural history of genital HPV infection in children is unknown. However, because the thin layer of columnar epithelium that lines the lower genital tract during childhood and early adolescence may be more vulnerable to HPV infection than the complex, multilayer, squamous epithelium that lines these structures during later adolescence and adult life,²⁵⁻²⁸ early exposure to these oncogenic viruses

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could increase the risk of developing dysplastic or malignant genital lesions later in life. Indeed, it has been suggested that some proportion of the rapidly increasing number of adolescent girls with HPV-associated intraepithelial lesions is attributable to infection acquired through childhood sexual abuse,^{14–16} especially given the apparently frequent and substantially underreported nature of this problem.²⁹

To address these gaps in our knowledge about the source and natural history of pediatric HPV infections, we studied the prevalence of genital HPV infection in a population of sexually abused and nonabused preadolescent girls and assessed the feasibility of conducting a longitudinal study of the natural history of these infections in this population.

METHODS

Participants

The study sample consisted of a racially and ethnically diverse group of 41, 5- to 12-year-old girls (mean \pm standard deviation [SD] = 8.9 \pm 2.4 years), who were referred to the Child Advocacy and Protection Team (CAP Team) at Children's Hospital in Denver, Colorado, for evaluation of sexual abuse between September 1995 and March 1996. We chose this population for study to minimize the likelihood of encountering HPV infections acquired through vertical transmission, nonsexual horizontal transmission, and consensual sexual contact among teenage peers.^{2–16} Eligible children and their guardians were given the opportunity to participate in both a cross-sectional HPV prevalence study and a longitudinal HPV natural history study. Both studies were approved by the Institutional Review Board at the University of Colorado Health Sciences Center.

Sexual Abuse Assessment

The CAP Team is a multidisciplinary group that consults on cases of suspected child abuse and neglect. The team is led by pediatricians with subspecialty training in child abuse. Social workers, nurses, psychologists, child psychiatrists, and attorneys also participate. The team's routine evaluation includes: interviews with identified children and their caretakers, a review of previous medical and social service records, a forensically acceptable physical examination, and additional diagnostically appropriate laboratory and radiologic studies. Decisions about testing individual children for sexually transmitted diseases, semen, sperm, and acid phosphatase are made by the examining clinician. The team uses these collective data to define the following 3 categories of sexual abuse^{30,31}:

1. *Confirmed*: 1 or more of the following:
 - a. The child spontaneously discloses abuse to a disinterested party in a forensically acceptable manner.
 - b. The child had physical examination findings indicative of abuse such as acute or healed posterior hymen tears or circumferential anal fissures with anal swelling or bruising, in the absence of a history of accidental trauma that would account for the findings.
 - c. The child had a sexually transmitted disease other than HPV that was not contracted perinatally.
 - d. The perpetrator admitted to abuse.
 - e. A credible witness observed the abuse occurring.
 - f. A forensically acceptable physical examination revealed the presence of semen, sperm, and/or acid phosphatase.
2. *Ruled-out*: A medical cause was present for the physical examination findings that led to a suspicion of abuse, or a reasonable explanation was found for abnormal behavior or unusual statements.
3. *Suspected*: All others.

Study Procedures

After the completion of the routine CAP Team interview, study procedures were explained, and informed consent for participation was obtained. During the standard forensic medical exami-

nation that followed, 2 additional specimens were collected for HPV testing. The first specimen was obtained by gently rubbing a Dacron swab (Allegiance, McGraw Park, IL) over the surface of the labia, vaginal introitus, perineum, and perianal area.¹⁶ The second specimen was obtained by inserting a flexible, small bore, plastic catheter through the hymenal opening and lavaging 10 mL of phosphate-buffered saline in and out of the vagina 2 to 3 times.¹⁴ After collecting the specimens for HPV testing, a 5% acetic acid solution was applied to the vulva and perineum for 5 minutes and the area was examined for genital warts and colposcopic evidence of HPV infection (eg, aceto-white areas with distinct borders and raised granular surfaces, mosaicism, punctations, and/or abnormal vessel patterns; areas of diffuse aceto-whitening and papillomatosis were not considered evidence of subclinical HPV).^{12,18,32} Direct intravaginal visualization was not attempted and no Papanicolaou smears or biopsies were obtained.

Laboratory Studies

After agitation in normal saline, the surface samples were transported with the lavage samples to the laboratory. The samples were spun for 10 minutes at 15 K, the pellet was resuspended in 500 μ L of normal saline, and the cells were counted using a standard hemocytometer. The samples were then respun at 15K for 10 minutes and the pellet resuspended in 1 mL of Digene Sample Transport Medium (Digene Diagnostics, Silver Spring, MD) and stored at -20°C for batched DNA extraction. DNA was extracted by 2 ethanol precipitations, followed by resuspension in 100 μ L of sterile water and the samples were stored at -20°C for subsequent polymerase chain reaction (PCR) analysis. Full details of the laboratory procedures are published elsewhere.^{34–36} Briefly, PCR amplification was performed with the degenerate L1 consensus primer pairs MY09 and MY11 (the latter 5' biotinylated) in a 100- μ L mixture of 1U of *Taq*-polymerase (Amplitaq) for 40 step cycles (1 minute at 94°C , 2 minutes at 55°C , and 3 minutes at 72°C).⁴⁰ Amplimers were detected using the SHARP Signal System (Digene Diagnostics, Silver Spring, MD) as described by the manufacturer and others.^{41,42} Five μ L of control and sample were denatured with base and then allowed to hybridize with probe mixtures containing either low-risk (6,11,42,43,44) or high-risk (16,18,31,33,35,39,45,51,52,56,58) HPV types. Immobilized RNA: DNA hybrids, were captured on a streptavidin-coated plate and then exposed to an antihybrid antibody conjugated to alkaline phosphatase and detected with paranitrophenylphenol. Color intensity was determined by colorimetric reader at 405 to 410 nm. To determine sample adequacy, amplification of β -globin was performed using DNA oligonucleotides PC04 and GH20 (Research Genetics, Huntsville, AL), and amplimers were detected exactly as the HPV amplifications were, using RNA probes manufactured by Digene Diagnostics (Silver Spring, MD). Throughout the study RNase-free pipette tips and tubes were used and sample negative controls remained negative. Laboratory studies were performed without prior knowledge of clinical data.

Longitudinal Data Collection

Families who agreed to participate in the longitudinal HPV natural history study received a telephone call from a research assistant within 2 weeks of their CAP clinic visit. The research assistant was a community service worker who was familiar with the local culture and had extensive practical outreach experience with high-risk families. During her initial contact with the family the research assistant reviewed the results of the clinic evaluation and explained that she would be contacting them monthly to see if the child had developed genital warts or other lower genital tract symptoms. Follow-up examinations were scheduled in the general pediatric clinic at Children's Hospital at 4-month intervals for 2 years.

Data Analysis

Univariate analyses were used to describe the study population and the frequency of HPV infection and colposcopic abnormalities. Comparisons between abused and nonabused and HPV-positive and HPV-negative children were conducted with Student's *t* tests, χ^2 tests, and Fisher's Exact tests, as appropriate. All statistical analyses were performed with SPSS/PC+.³⁷

RESULTS

During the study period the CAP Team evaluated 62, 5- to 12-year-old girls, 41 (86%) of whom were enrolled in the study. The remaining 21 girls did not enroll; 8 refused to participate, 5 mothers refused to allow their daughters to participate, 2 case workers were unable to give consent for participation, and 6 children were inadvertently missed by the study staff. Nonparticipants were significantly younger than participants (mean \pm SD = 7.3 ± 2.4 years compared with 8.7 ± 2.4 years; $P = .02$). One child's samples were lost in processing, leaving 40 evaluable participants, among whom sexual abuse was confirmed in 29 (72.5%), suspected in 2 (5%), and ruled out in 9 (22.5%). Only 3 (10.3%) of the 29 children with confirmed abuse had an abnormal genital examination. In all cases abnormalities were limited to hymenal bruises or tears. In the remaining 26 cases the diagnosis of sexual abuse was based on disclosure by the perpetrator or a credible report by the child or a witness who observed the abuse occurring. None of the girls had clinically apparent warts or colposcopic findings suggestive of subclinical HPV infection.

Specimens obtained by the surface swab and vaginal lavage sampling techniques contained similar amounts of cellular material, with a mean of $3.5 \pm 4.4 \times 10^5$ cells/mL (range: $0-16.0 \times 10^5$ cells/mL) for the swab samples and $3.0 \pm 6.0 \times 10^5$ cells/mL (range: $0-24.0 \times 10^5$ cells/mL) for the lavage samples. Human β -globin sequences were detected in 95% ($N = 38$) of the swab samples and 98% ($N = 39$) of the lavage samples and at least 1 β -globin-positive sample was obtained from each of the 40 study participants. β -globin-positive swab and lavage samples contained more cells ($3.6 \pm 4.5 \times 10^5$ vs $3.0 \pm 6.0 \times 10^5$ cells/mL) than β -globin-negative samples ($1.0 \pm 1.2 \times 10^5$ and 0 cells/mL, respectively).

As shown in Table 1, HPV DNA was detected in 5 children (13%) of the 38 β -globin-positive swabs and 2 (5%) of the 39 β -globin-positive lavages contained HPV DNA. There was no significant difference in the mean number of cells in the HPV-positive and HPV-negative samples ($3.1 \pm 4.2 \times 10^5$ compared with $4.9 \pm 6.0 \times 10^5$ cells/mL). Four (80%) of the 5 HPV positive samples contained only low-risk types of HPV and 1 sample contained only high-risk types of HPV.

HPV DNA was detected in 5 (16%) of the 31 girls with confirmed or suspected sexual abuse and none

of the 9 nonabused girl ($P < .05$, Fisher's Exact test). The HPV-positive and HPV-negative sexually abused girls did not differ significantly in age (mean \pm SD = 8.9 ± 1.9 and 8.8 ± 2.6 years, respectively). Table 2 outlines the association of detection of HPV DNA among the 31 girls with confirmed or suspected sexual abuse by age and sexual abuse characteristic. Although the small numbers limit the ability to assess associations, there is no clear relationship between age or sexual abuse characteristic and the detection of HPV DNA. Of note, HPV DNA was not detected more frequently in those with abnormal physical findings or who described genital-genital sexual contact than in abused girls without these characteristics.

Of the 40 girls who participated in the cross-sectional HPV prevalence study, 20 (50%) agreed to participate in the longitudinal, natural history study. The research assistant established telephone contact with all 20 families and remained in contact with the majority of them for 3 to 4 months. Most caretakers (parents or legal guardians) were receptive to her calls and expressed interest in the results of the study. However, despite numerous attempts to schedule appointments, none of the families returned for further evaluation.

DISCUSSION

The results of this study indicate that subclinical genital HPV infection is common among sexually abused 5- to 12-year-old girls whereas genital warts and colposcopically apparent HPV infections are not. Our finding that 5 (16%) of the 31 girls who had been or were suspected to have been sexually abused and none of the 9 girls in whom sexual abuse was ruled out had subclinical genital HPV infection is consistent with the only other published comparison of the prevalence of genital HPV infections in sexually abused and nonabused girls. Gutman and colleagues¹⁴ reported that vaginal wash samples obtained from 15 severely sexually abused girls were significantly more likely to contain HPV DNA (by Southern blotting) than samples from nonabused controls (33% compared with 0%). By contrast, in a more recent and larger study, Siegfried and colleagues¹⁶ were able to identify HPV DNA (by PCR) in only 2 (3%) of 40 likely sexually abused children. It is more difficult to compare the results of the latter study to our own as it did not include a control group, and the study population contained 11 males

TABLE 1. Comparison of HPV DNA Detection by Vulvar Swab and Vaginal Lavage in Abused and Nonabused Girls

Variable	Swab Sample		Lavage Sample		Total	
	Abused	Nonabused	Abused	Nonabused	Abused	Nonabused
Number	31	9	31	9	31	9
β -globin-positive (N)	30	8	31	8	31	9
HPV-positive (N)*						
High-risk type	1 (3%)	0	0	0	1 (3%)	0
Low-risk type	2 (7%)†	0	2 (6.5%)	0	4 (13%)	0
Any HPV	3 (10%)	0	2 (6.5%)	0	5 (16%)‡	0

* High-risk types: 16,18,31,33,35,39,45,51,52,56,58; low-risk types: 6,11,42,43,44.

† Percent of β -globin-positive samples.

‡ $P < .05$; abused vs nonabused, Fisher's Exact test.

TABLE 2. Comparison of HPV DNA Detection by Vulvar Swab and Vaginal Lavage in Abused and Possibly-Abused Girls

Variable	Number	Swab Sample	Lavage Sample	Total
Age group N (%)				
5-8 y	16	1 (6.3)	1 (6.3)	2 (13)
9-12 y	15	2 (13)	1 (6.7)	3 (20)
Basis of abuse diagnosis*				
Definite abuse N (%)				
Examination abnormal	3	0	0	0
Disclosure/examination nl	26	2 (7.5)	2 (7.5)	4 (15)
Possible abuse N (%)	2	1 (50)	0	1 (50)
Type of abuse N (%)				
Genital/genital	15	0	1 (6.7)	1 (6.7)
Other	16	3 (19)	1 (6.3)	4 (25)

* See text for definitions.

and 6 teenage girls. Indeed, limiting their analysis to the 20 5- to 12-year-old girls with β -globin-positive vulvo-vaginal samples yields an HPV prevalence of 10% (2/20), closer to the 16% prevalence of genital HPV DNA found in the abused portion of our population. Finally, it is important to note that we collected 2 samples from each participant (a vulvo-perineal surface swab and a vaginal lavage) whereas Siegfried and colleagues collected only a vulvo-perineal surface swab sample. Although we found the 2 collection techniques equally effective (as assessed by cell counts and β -globin positivity), the HPV results were additive (eg, none of the girls had detectable HPV DNA in both samples). This may reflect a real difference in the prevalence of HPV at the 2 test sites or simply the widely recognized sampling problems inherent in the collection of genital cellular material.¹⁸⁻²² In either case, our findings suggest that published data may underestimate the prevalence of subclinical HPV infections in sexually abused preadolescent girls.

Our disappointing follow-up rate points to the difficulty involved in studying the natural history of genital HPV infections in preadolescent, sexually abused girls. Unfortunately, this is not a unique experience. Studies of adult rape victims indicate that only a minority of those who agree to return for follow-up counseling actually do so.³⁸ It is understandable that most sexually abused persons want to distance themselves from abuse evaluations as quickly as possible. However, this situation means that it will be difficult to prospectively study a group of HPV-infected children that is large enough to accurately assess the effects of age and reproductive tract immaturity on the natural history of genital HPV infection. Instead, it may be necessary to draw inferences from studies of girls who voluntarily initiate sexual activity soon after menarche. The relatively large cervical ectropion and paucity of protective cervical mucous that are characteristic of the lower genital tract during early adolescence are thought to increase the vulnerability of these structures to environmental carcinogens.²⁸ Thus the perimenarcheal cervix may be a good model for studying the effect of epithelial cell immaturity on the natural history of genital HPV infection.

Although genital HPV is present in a substantial minority of sexually abused girls, current data do not

appear to justify the inclusion of HPV screening in the initial evaluation of children with suspected sexual abuse. Because considerable uncertainty still surrounds the mode of HPV transmission in children,²⁻¹⁶ particularly in very young children (among whom vertical transmission at birth and nonsexual horizontal transmission during bathing or diapering are potential sources of genital HPV infections), genital HPV is not specific enough for sexual contact to be considered an abuse defining sexually transmitted disease like gonorrhea or chlamydia.³⁹ Even HPV testing with type-specific assays is apt to be of limited value because it does not clearly define whether the mode of transmission was abusive or not.^{6,7} Furthermore, because the majority of sexually abused 5- to 12-year-old girls do not have detectable genital HPV infection, it is not a sensitive indicator of abuse.^{14,16} However, in view of the difficulties associated with characterizing the natural history of genital HPV infections in sexually abused girls, it may be appropriate to initiate Pap smear screening when they reach adolescence, even if they have not yet initiated voluntary sexual activity.

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