Human Papillomavirus Infections in Children

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The human papillomavirus (HPV) causes anogenital warts (condylomata acuminata) in adults and children. Anogenital warts were once a rare pediatric infection with only 34 cases reported prior to 1982. The increasing number of infected children parallels the explosive epidemic of adult HPV disease that began in the mid-1960s.

The medical evaluation and management of HPV infection in children is complicated by a long viral latency period, several possible modes of transmission including sexual transmission, and no single effective treatment regimen. Human papillomavirus also is associated with cervical, anal, and penile carcinomas in adults. Affected children are at potential risk for the development of such cancers. This article reviews the basic molecular biology of HPV, its major manifestations, evaluation, and treatment of infections in children.

BACKGROUND

The human papillomavirus is a nonenveloped, icosahedral, double-stranded deoxyribonucleic acid (DNA) virus of the family Papovaviridae. With the advent of recombinant DNA technology in the mid-1970s and the cloning and sequencing of HPV DNA, multiple types of HPV were identified. A new virus isolate is considered to be a distinct type if it contains less than 50% homology with known viral types. Approximately 70 viral types have been described. The association of different HPV types with specific sites of infection is now well known. Types 1 and 4 are associated with plantar warts, with type 2 isolated from common warts. Types 6 and 11 are found most often in grossly apparent genital condyloma acuminata, laryngeal papillomas, and conjunctival infections. Types 16, 18, 31, 33, and 35 also infect the genital tract as cervical flat warts and cervical atypia. These are the types that not only can cause anogenital cancers but also have been reported in squamous cell carcinomas of the respiratory tract and at other cutaneous sites. Several types are associated with a rare, autosomal recessive dermatologic condition, epidermodyplasia verruciformis, in which affected individuals demonstrate a strong tendency to develop multiple wart-like lesions caused by HPV.
HISTOPATHOLOGY

Human papillomavirus is an epitheliotrophic virus. It attacks the nucleus of squamous epithelial cells, entering at the basal layer of the epidermis presumably at sites of microtrauma. The result is hyperplasia of basal and parabasal cells (acanthosis), degenerative cytoplasmic vacuolization (koilocytosis), and variable thickening of the more superficial epidermal layers (hyperkeratosis and parakeratosis). The nucleus may demonstrate binucleation, pyknosis, and wrinkling.2

DETECTION OF HPV

Human papillomavirus has defied attempts to be cultured, therefore a variety of clinical, histological, and cytological methods have been developed in order to detect active infection. Visual inspection has been aided by colposcopy, magnification, and the application of acetic acid that highlights involved tissue. Histologic and cytologic evaluation of tissue specimens by light microscopy are useful for determining if the typical epithelial abnormalities caused by HPV are present, but does not detect subclinical or latent infection. Human papillomavirus DNA has been found to exist in normal tissues adjacent to the lesions.7 The most sensitive techniques are those that actually detect small amounts of HPV DNA. In situ hybridization uses a labeled ribonucleic acid or DNA probe to detect HPV DNA in a specimen. Specific viral typing in this method is unreliable, and recognition of a false-positive assay may be difficult.8 In situ hybridization will detect 20 copies of HPV DNA per cell.9

Southern blot hybridization with restriction endonuclease pattern analysis is considered the gold standard of HPV detection: it is very sensitive and provides specific HPV typing.2 It will detect as little as 0.1 copies of HPV DNA per cell. Southern blot technique is very time and labor intensive and is not practical for routine screening.10 Dot/blot techniques using commercially available kits (ViraPap and Vira-Method: Digene, Gaithersburg, Maryland) have been developed to detect seven HPV types and have the sensitivity of Southern blot with the advantage of rapid screening at less cost.2

Gene amplification technique using the polymerase chain reaction (PCR) will detect as little as one genome of HPV DNA per 100 000 cells.10 This method appears to be extremely sensitive and useful with very small samples sizes. Whether these minute amounts of DNA eventually will lead to clinical disease is not known. Due to the enormous amplification of DNA, contamination of specimens resulting in false positives can be a problem and is currently an area of intensive investigation.9,11

CLINICAL PRESENTATION

Pediatric anogenital HPV infection typically pre-
sents as verrucous, flesh-colored or reddish papules that may be flat, grouped, pedunculated, or coalesce to form large lesions. The most common location of condylomata acuminata in either sex is perianal (Figure 1). The lesions may extend into the anal canal. In females, condylomata acuminata occur around the urethra, hymen, posterior fossa, or fourchette and appear irregular or as multiple small papules (Figures 2 and 3). Lesions may spread onto the skin of the labia minora and majora. Because internal examinations are not routine in prepubertal girls, vaginal and cervical warts are rarely described, but vaginal washings of sexually abused girls have been found to contain HPV DNA.12

Prepubertal males occasionally have penile lesions around the corona, urethra, or on the shaft. Although scrotal lesions are common in adults, they only occasionally occur in boys and may have a flatter, more papular appearance. Condylomata acuminata often are asymptomatic, only being discovered during diaper changes, toileting, or physical examinations. The lesions may grow and spread rapidly, remain stable, or spontaneously regress with time. Neither the clinical appearance nor the exuberant growth of lesions has been associated with a particular mode of transmission. Symptoms may occur when the lesions become friable or irritated due to trauma. They then can become infected resulting in pain, pruritus, or bleeding and cause dysuria and vaginitis in girls.

To an experienced examiner, the typical clinical appearance and location of the lesions may be diagnostic of condylomata acuminata. However, other conditions, which have very different implications for the child, have been mistaken for condylomata acuminata, such as molluscum contagiosum. Molluscum can occur exclusively in the anogenital area and become grouped or clumped simulating the verrucous appearance of condylomata acuminata (Figure 4). A careful examination of the child and siblings for typical pearly papules with central umbilication may be helpful in making this diagnosis.

Other conditions that may resemble condylomata acuminata include condyloma lata, chronic benign pemphigus, histiocytosis X, neurofibromatosis, pseudoverrucous papules and nodules, Bowenoid papulosis, and other neoplasms (Table 1). A rapidly developing or intractable condylomata acuminata may indicate underlying immunosuppression such as infection with human immunodeficiency virus.13

Human papillomavirus may present in children at extragenital sites, such as the oral cavity and conjunctiva, and larynx. Laryngeal papilloma is the most common type of benign pediatric laryngeal tumors.14 Laryngeal papillomas may be difficult to diagnose, presenting as cough, hoarseness, croup, or upper airway obstruction. This can lead to significant morbidity and even mortality. Direct laryngoscopy reveals typical verrucous lesions on or around the vocal cords. The lesions often recur, require multiple treatments, and can develop into carcinomas.

DIAGNOSIS
A clinical impression based on the appearance and location generally is sufficient to make the diagnosis of anogenital condylomata acuminata in most cases. Tissue biopsy of questionable lesions may be necessary to differentiate anogenital warts from other conditions. This may be difficult in the pediatric outpatient setting unless the lesion is pedunculated and can be excised quickly. Tissue biopsy should be reserved for those cases in which the diagnosis is in doubt or the child is undergoing general anesthesia for wart removal. A Papanicolaou smear for cytologic analysis or dot/blot analysis of the lesion may be performed. New techniques that use PCR analysis require only a

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superficial scraping or swab of the lesion. This method remains mostly a research tool.

Human papillomavirus DNA typing has been performed to clarify the source of infections and to understand the epidemiology of HPV in children. Viral typing is helpful in determining if a lesion contains genital or nongenital types, but does not assist in determining the mode of transmission. Human papillomavirus types in condylomata acuminate in children are similar to those found in adults, the majority being types 6 and 11, with types 16 and 18 occasionally reported (Frasier LD, Jenny C. 1990. Unpublished data).15-19

Children infected with HPV type 16 or 18 at birth or during childhood may be at risk for developing carcinoma. Bowenoid papulosis is a premalignant condition that has been described in at least four children, including an 8-year-old male in our clinic (Figure 5).20 The duration of viral infection may increase the risk of oncogenic change, and a child has potentially many more years of exposure to HPV than adults who acquire it through sexual relations. As a result, clinicians should be alert to the need for long-term follow-up of children with anogenital HPV infections.

MODES OF TRANSMISSION

Unlike the adult population where HPV is almost exclusively a sexually transmitted disease, other modes of transmission may occur in children. These include vertical transmission (prenatally or perinatally), auto- or heteroinoculation from digital or other lesions, casual contact via fomites, and sexual abuse.8

Vertical Transmission

Several case reports of infants born with condyloma acuminate support prenatal transmission of the virus.13,21,22 The transmission of HPV at birth through an infected birth canal is the presumed source of juvenile laryngeal papillomias and anogenital disease.23 Both conditions present in infancy or early childhood. A small percentage of newborn infants are found to have HPV DNA in the mouth, the anus, or the foreskin.22,24 This represents a viral inoculation with potential for causing infection. The risk of a child developing anogenital condylomata acuminate from an HPV-infected mother is not known.

The latency period between possible infection at birth and manifestation of vertically acquired anogenital warts is controversial. Most authors accept a 1-year period. Others suggest the virus can be latent up to 3 years or perhaps longer.8 Additionally, when a child presents with condylomata acuminate at several months to years following birth, it is difficult to determine if the mother was infected at the time of delivery. A clear prenatal history of genital warts, cervical atypia, or cervical cancer may be reassuring if sexual abuse has been appropriately investigated. Maternal infections with HPV can regress spontaneously, complicating attempts to retrospectively document vertical transmission.

Another mechanism of viral transmission is via inoculation from common or hand warts, or autoinoculation. As noted previously, HPV type 2 rarely has been found in the genital area. However, fondling is a common form of sexual abuse, especially in younger children. The presence of type 2 HPV does not necessarily indicate “innocent” transmission as is suggested in some studies.

Casual Transmission

Casual transmission has been proposed to occur as the result of infected secretions coming into contact with the child through sharing of towels, bathing
TABLE 3

Screening for Sexually Transmitted Diseases: Recommendations of the Centers for Disease Control and Prevention

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<tr>
<th>Females</th>
<th>Males</th>
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<tr>
<td>● Culture pharynx, anal canal, and vagina for Neisseria gonorrhoeae and Chlamydia trachomatis</td>
<td>● Neisseria gonorrhoeae and Chlamydia trachomatis cultures of pharynx, rectum, and urethra</td>
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<tr>
<td>● Culture vagina and examine urine for Trichomonas vaginalis</td>
<td>● Herpes simplex cultures from areas of inflammation</td>
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<td>● Serologic test for syphilis</td>
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<td>● Examine for venereal warts</td>
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Adapted from the Centers for Disease Control.29

Sexual Transmission

Sexual transmission of HPV to children is a significant source of infection in all age groups. Approximately 1 in 4 girls and 1 in 8 to 10 boys are sexually abused prior to the age of 18.25 There is considerable disagreement in the literature regarding the prevalence of sexual abuse in children presenting with anogenital warts. In several reported series, between 10% and 91% of children evaluated for anogenital condyloma acuminata were suspected of being sexually abused.15-17,26 These widely discrepant figures depend on how the evaluation for sexual abuse was undertaken. They also may represent "referral bias" in the studies. The highest prevalence of abuse is noted when comprehensive assessments for sexual abuse are done.26 This includes behavioral assessments, careful interviewing of the child by an experienced professional, and a forensic genital evaluation for evidence of genital trauma and other sexually transmitted diseases.

A study by McCann et al17 found no anogenital warts in children who were screened and determined not to have been sexually abused. Additionally, a North Carolina study showed 33% of patients confirmed to have a history of sexual abuse had vaginal washings positive for HPV, while a control group of nonabused girls had no HPV-positive washings.12 These and other studies suggest sexual abuse should be ruled out in any child presenting with anogenital warts.

EVALUATION

Table 2 summarizes the American Academy of Pediatrics guidelines for the evaluation of sexual abuse in children.28 Because condylomata acuminata is considered a sexually transmitted disease, a laboratory evaluation of other sexually transmitted diseases should be undertaken following recommendations of the Centers for Disease Control and Prevention (Table 3).29 An evaluation of the social environment and other caretakers of the child is important, but often is beyond the scope of the physician and so requires reporting to child protective services.

Even under optimal circumstances, it may be difficult to determine how the HPV was acquired, and other modes of transmission may be considered. An indeterminate investigation for sexual abuse is not proof that it did not occur. The majority of children with a history of sexual abuse will have normal genital examinations; therefore, the history from the child is of utmost importance.30 However, even children with unequivocal evidence of abuse may not be able or willing to disclose their history. Perhaps the most difficult group to evaluate is that of preverbal children who cannot give a history. These children and infants fall into the age range where vertical transmission is possible and sexual abuse cannot be proven by a comprehensive evaluation. The presence of condyloma acuminata alone with no other historical, behavioral, or physical indicators is not proof of sexual abuse, but should be viewed as a suspicious finding. Careful follow-up of any child with condyloma acuminata is warranted regardless of the outcome of the investigation.

TREATMENT

The presence of anogenital warts on a child can be distressing to parents and caretakers. Although not highly contagious in children, there is the perception that children with anogenital warts present an infection risk to others. Often, there is an urgency on the part of parents to desire an immediate treatment that will cure the disease.

Because HPV is known to be present in normal
epithelium adjacent to histologically abnormal cells, eradication of subclinical and latent virus is impossible. As a result, all treatment modalities have as high as 50% failure rates. Additionally, most treatments are topical and involve caustic or irritating agents such as liquid nitrogen, trichloroacetic acid, or podophyllin. These agents are often painful or uncomfortable and poorly tolerated by a child who may have to undergo multiple applications. Systemic, lesional, and topical interferon have been investigated and are associated with undesirable side effects and similar rates of recurrence. Also, anogenital warts may resolve spontaneously at a rate similar to that of successful treatment.

Ablation of condyloma acuminata by carbon dioxide, laser, or electrocautery in children is a procedure requiring general anesthesia and should be reserved for those lesions that are too extensive to treat topically, are causing discomfort or other symptoms, or are recalcitrant to more conservative therapy. Laser treatment also may be considered if biopsy or internal examination under general anesthesia is indicated. These methods, when performed by physicians experienced in the management of children, have few side effects, little postoperative pain, and minimal scarring. However, the long-term cure rate is no better than that seen with more conservative forms of treatment. Subjecting the child to a general anesthesia for removal of minor, asymptomatic lesions is not indicated.

The parent and, if appropriate, the child should be informed of the risks, benefits, and limitations of any treatment plan proposed. If the lesions are not symptomatic or cosmetically distressing, the clinician could reasonably choose not to treat them. A more aggressive approach is reasonable if the child has a potentially oncogenic type 16 or 18, although there is no data that suggests treatment affects long-term outcome.

**SUMMARY**

Human papillomavirus infections in children, particularly when occurring as condyloma acuminata, present a difficult and often puzzling problem. The possibility that the lesions were acquired through sexual contact mandates a careful and thorough evaluation. Even then, the source of the infection may be elusive because of a long latency between inoculation and the development of lesions, the secretive milieu of childhood sexual abuse, and lack of data about modes of transmission. New molecular techniques of HPV DNA detection and typing have not proven to be helpful in determining the source of the infection but may assist in identifying children who are at risk for the development of carcinoma. Various treatment modalities have been attempted with a significant percentage of recurrences. Many unanswered questions remain regarding the biology and epidemiology of HPV in children and adults. Clinical and basic science research specifically designed to address the concerns of the pediatric age group is urgently needed.

**REFERENCES**