Eur J Pediatr (2009) 168:267–273
DOI 10.1007/s00431-008-0882-z

REVIEW

Human papilloma virus (HPV) infection in children and adolescents

Ioannis N. Mammas · George Sourvinos · Demetrios A. Spandidos

Received: 25 July 2008 / Revised: 23 September 2008 / Accepted: 13 November 2008 / Published online: 3 December 2008

Abstract Human papilloma viruses (HPV) are common pathogens associated with a wide range of cutaneous and mucosal infections in childhood. Different HPV types can cause common warts, genital warts, low-grade as well as high-grade squamous intraepithelial lesions. Anogenital warts represent an issue with legal and clinical implications and evaluation of children for the possibility of sexual abuse should be considered in all cases. Recurrent respiratory papillomatosis has also been associated with HPV infection in a variety of studies. The recently introduced HPV vaccination is expected to prevent HPV-related cervical cancer in adulthood; however, HPV infection will continue to affect children.

Keywords HPV infection · Children · Warts · Recurrent papillomatosis · Cervical neoplasia · HPV vaccine

Abbreviations

HPV	human papilloma virus
SIL	squamous intraepithelial lesion
RRP	recurrent respiratory papillomatosis

Introduction

Human papilloma viruses (HPV) are small double-stranded DNA viruses that comprise a family of more than 130 types [32, 50, 70]. HPVs can be classified into mucosal and cutaneous types [62]. Mucosal types infect the mucous membranes and can cause cervical neoplasia in adults as well as anogenital warts in both children and adults. 'High-risk' HPV types have been implicated in the development of SILs and their progression to cervical cancer [11, 37, 41, 70]. Mucosal HPV types 16 and 18 represent the most frequent 'high-risk' types that are detected in female anogenital system and are detected in more than 70% of women with cervical cancer [11]. 'High-risk' and 'low-risk' mucosal HPVs have also been involved in the development of SILs, while 'low-risk' types 6 and 11 cause approximately 90% of the cases of genital warts [11, 70]. Cutaneous types infect the squamous epithelium of the skin and produce common warts, plantar warts, and flat warts, which occur commonly on the hands, face, and feet. Specific cutaneous types are also detected in *epidermodysplasia verruciformis*, a rare familial disorder that is related to the development of large cutaneous warts that can progress to skin cancer [28], and WHIM syndrome, a rare combined immunodeficiency syndrome which is characterized by warts, hypogammaglobulinemia, recurrent bacterial infections, and myelokathexis [22].

Although HPV infection is considered a sexually transmitted infection, HPVs can also be transmitted by non-sexual routes including casual physical contact and perinatal vertical transmission [54, 64]. The virus infects primarily epithelial cells through abrasion of the skin or the mucosa, where it can exist as a long-term latent infection that can reactivate or persist [54]. In the majority of individuals, HPV infection remains transient and asymptomatic and, in most cases, HPV infection resolves within 2 years [58]. As demonstrated in Fig. 1, several factors are thought to play a role in the progression of HPV infection, including individual susceptibility, immune status and nutrition, endogenous and exogenous hormones, tobacco

I. N. Mammas · G. Sourvinos · D. A. Spandidos (✉)
Department of Virology, School of Medicine, University of Crete, Heraklion,
71100 Crete, Greece
e-mail: spandidos@spandidos.gr

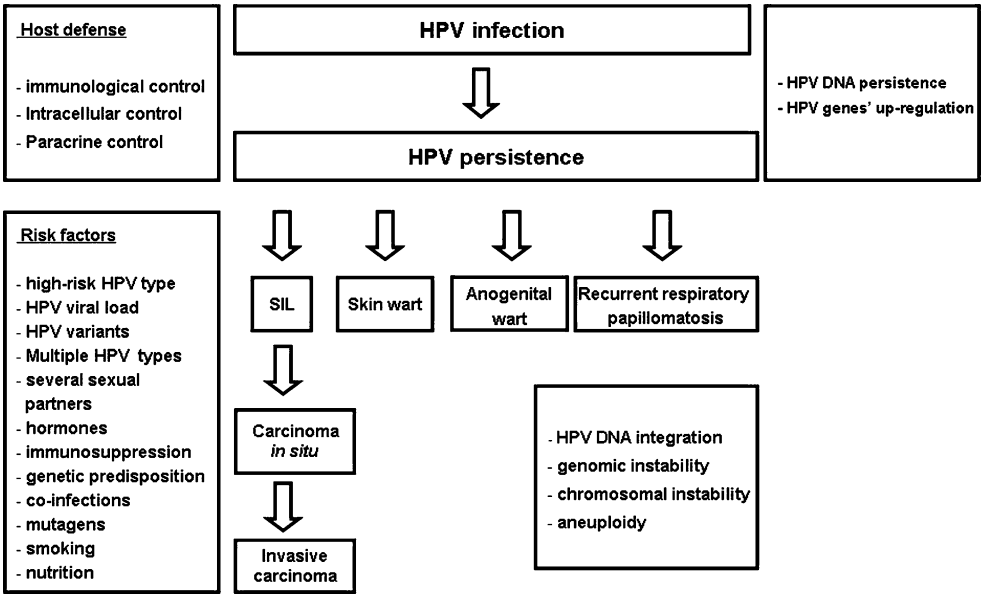

Fig. 1 Progression of HPV infection

smoking, parity, co-infection with other sexually transmitted agents such as HIV, herpes simplex virus type 2, and *Chlamydia trachomatis* as well as viral characteristics such as HPV type, concomitant infection with other types, viral load, HPV variant, and viral integration [7, 58].

Skin warts

Skin warts are considered the main manifestation of the cutaneous HPV types, with HPV 1, 2, 3, 4, 27, and 57 being detected most frequently [10, 43] (Table 1). Although cutaneous HPV types are predominantly detected in skin warts, the presence of mucosal HPVs has also been reported; however, the origin and the role of these types on the skin remain unclear [10, 31, 43]. Skin warts exist in different forms including common warts (*Verruca vulgaris*), plantar warts (*Verruca plantaris*), and flat warts (*Verruca plana*). Skin warts are estimated to occur in up to 10% of children and young adults, with the greatest incidence between 12 and 16 years of age [43]. Warts occur more frequently in girls than in boys. Common warts represent 70% of skin warts and occur primarily in children, whereas plantar and flat warts occur in a slightly older population [42].

Table 1 Different benign and premalignant lesions and the associated common HPV types in childhood

Lesions	HPV types
Skin warts	1, 2, 3, 4, 27, 57
Anogenital warts	11, 6, 2, 3
Asymptomatic oral infection	11, 6, 16, 18
Recurrent respiratory papillomatosis	11, 6
Cervical neoplasia	16, 18

It has been proposed that HPV infection of normal skin is acquired very early in infancy [3]. In most cases, among healthy individuals, cutaneous HPV types rise to persistent subclinical infections without causing warts or other lesions of the skin [21]. The natural progression of skin warts in childhood indicates that warts spontaneously clear after 2 years without treatment in 40% of children. Depending on their location, warts can be painful, e.g., in soles of the feet or near the nails, while in other cases are viewed as socially unacceptable when they are located on visible areas, e.g., in hands or face [59].

Management–treatment To date, many different approaches to wart therapy exist as no single therapy has been proven effective at achieving complete remission in every patient [5, 53]. These include salicylic acid, cryotherapy, laser therapy, imiquimod, bleomycin, retinoids, and immunotherapy. Treatment choice should be determined by the distribution, the size and the number of the lesions, the age, prior treatments, the ability of the child and the parents to tolerate and comply with treatment recommendations, the comorbid conditions, and the potential adverse reactions [57].

Anogenital warts

Anogenital warts in children are rare, much less common than in adults; however, in pre-pubertal children, the reported incidence has been increasing dramatically since 1990 [4, 49]. In girls, anogenital warts can present in the vulvar, vaginal, urethral, and peri-anal areas. In boys, typically genital warts are located in the peri-anal area, while penile warts are rare. Girls present three times more often with anogenital warts than boys [1]. The clinical appearance of

anogenital warts varies from subtle, skin-colored flat warts to moist, pink to brown lesions found particularly in the skin creases and around the vaginal and anal openings [12]. HPV 11 and 6 are the most frequently detected HPVs in anogenital warts in children [4, 39, 40]. Cutaneous HPV types like HPV 2 or 3 are also detected; however, their incidence is low [39, 40]. Among non-sexually abused children with anogenital warts, cutaneous types are more common in older children aged over 4 years, in those with a relative who had skin warts, and in children with skin warts in other anatomical sites [40]. In contrast, mucosal types are more common in girls, in children under 3 years, in children with relatives with genital warts, and in those with no warts elsewhere [40].

The modes of HPV genital transmission in children remain controversial. HPV can reach a child's anogenital area by vertical transmission or by close contact, which can be either sexual or non-sexual [23, 49]. Sexual contact has been proposed as the most common mode of genital transmission of HPV in childhood by several researchers [23, 49]. In the study of Stevens-Simon et al. [60], genital HPV infection was found to be more common among sexually abused than non-sexually abused girls and the majority of them remained subclinical. However, recent studies suggest that, although sexual contact is a possible cause of HPV transmission, other pathways seem to be more likely including perinatal transmission, autoinoculation and heteroinoculation, and, possibly, indirect transmission via fomites [55, 64]. It has been found that the rate of anogenital warts among non-abused children was comparable with the rate reported in abused children [38]. Interestingly, 'high-risk' HPVs have been detected in 4–15% of genital samples obtained from asymptomatic infants, with a decreasing genital HPV DNA carriage rate during the first year of life [48]. HPV also appears to be common in asymptomatic pre-pubertal girls with no known vulval disease studied by Powell et al. [44].

Management–treatment Nevertheless, the presence of anogenital warts in children has serious social and legal implications as it raises concerns of possible sexual abuse [14, 23, 49]. The likelihood of sexual abuse, as the mode of acquisition, increases with the age in childhood [54, 55]. It is still not clear below which age sexual abuse is less likely to be implicated in cases of children with anogenital warts [55]. Every case needs to be evaluated in detail so as to determine whether enough concern exists to pursue additional investigations. It has been proposed that anogenital warts in children suggest abuse if the infection was not acquired perinatally; however, the time frame for perinatal transmission was not delineated [54].

The commonly used upper age limits for perinatal transmission are 12 to 24 months, while anogenital warts discovered among children more than 24 months of age are often assumed to have been acquired through sexual abuse. It is recommended that all children who present with anogenital warts should be evaluated by a consultant with expertise in child sexual abuse and children more than 4 years of age should be referred routinely to Child Protection Services [54]. In these cases, a multidisciplinary approach is advised for the proper care of children with anogenital warts [49]. Because of the long latency of HPV and the possibility of vertical and non-sexual transmission, it has been proposed that the best way to identify possible sexual abuse is by history taking, careful assessment of the socio-clinical context, and physical examination [34]. The modes of transmission of anogenital warts in children cannot be identified either by the clinical appearance of the lesions or by human papillomavirus typing. Most cases of anogenital warts in children are likely to be the result of non-sexual transmission, namely prenatal mode. Thus, these patients should be handled differently by the legal system unless other reasons for suspicion exist [25].

Spontaneous resolution of anogenital warts in children occurs in more than half of the cases and non-intervention has been suggested as a reasonable initial management approach [1]. Long-term follow-up for children with anogenital warts is recommended, although there are no longitudinal studies available to clarify whether they are at risk of developing carcinoma in young adulthood [24].

Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) in childhood occurs at an incidence of 0.3–3.9/100,000 and is considered as the most common benign tumor that affects the larynx in children [15, 68]. It is characterized by recurrent growth of benign papillomas along the epithelium of the upper respiratory tract including the larynx, the vocal cords, the arytenoids, the subglottis, and the trachea. The most commonly affected area is the mucocutaneous margin of the true vocal cords where the squamous epithelium of the vocal cord contacts the respiratory epithelium of the larynx. Exolaryngeal sites may become involved, including lungs, oropharynx, oral, and nasal cavity.

RRP is a potentially life-threatening benign tumor as it has the tendency to grow in size and number causing complete airway obstruction [65]. Children with RRP can present with hoarseness, variable degrees of chronic dyspnea, cough, stridor, dysphonia, or weak cry, with hoarseness being the most common presenting symptom [20, 69]. The duration of symptoms before definitive diagnosis varies from 2 months to more than 2 years. Early RRP can present solely with voice disturbance with or without stridor, including hoarseness, weak cry, and aphonia. The age of symptoms onset range from birth to 6 years old. RRP should be considered in children when other common pediatric airway diseases either do not

follow the natural history or do not respond to treatment. Diagnosis of RRP is confirmed by direct laryngoscopy and biopsy for tissue diagnosis.

The etiology of RRP is the infection of the upper airway with HPV types 6 and 11 [19, 20, 47, 51]. HPV infection is generally the result of perinatal transmission, implying that consideration of sexual abuse is unnecessary in RRP cases [55, 68]. Perinatal infection may occur transplacentally, via amniotic fluid during gestation and delivery and through direct exposure to cervical and genital lesions during birth. Rates of RRP are higher in firstborn children and those delivered vaginally than subsequent children or those delivered by Caesarian section [18]. Maternal history of anogenital warts, cytological or histological lesions of HPV infection in the genital tract, and maternal age less than 20 years are also associated with higher rates of RRP in children [18]. However, it is still unclear how frequently perinatal infection progresses to clinical lesions, whether genital, laryngeal, or oral.

RRP is characterized by a relatively low HPV viral load [29, 51]. Measures of HPV 6 and HPV 11 viral loads are relatively stable over time in most children with recurrent respiratory papillomatosis [26]. HPV 11 is considered as the most common cause of RRP [19, 47]. Children with RRP infected with HPV 11 are prone to develop more aggressive disease than HPV 6 and require more frequent surgical intervention [29, 52]. HPV 11 infection is also related to more frequent need for adjuvant therapies, tracheal and pulmonary disease, and tracheostomy [19, 47, 68].

Management–treatment The management of RRP depends on the degree of airway involvement and includes surgical removal, with high recurrence rates after treatment [68]. Various lasers, including CO_2, KTP, and pulsed dye, are the preferred method of surgical removal of RRP in children [66]. Adjuvant pharmacologic medical therapies with the antiviral agent cidofovir or interferon can also be used [20]. Affected children usually require multiple interventions with considerable impact on patients, their families, and the healthcare system accounting in the USA for an estimated 109 million dollar annual expenditure [65]. Surgical procedures for debulking frequently result in debilitating long-term dysphonia, laryngeal scarring, and rarely malignant degeneration [52]. Factors affecting the time course of RRP include: inter-surgeon variability, the extent and severity of papillomas at the time of laryngoscopy, and the use of adjuvant medical therapies [20].

Asymptomatic oral infection

To date, there are several studies that have demonstrated the presence of HPV DNA in the children's buccal cavity by studying oral swabs or washings from healthy asymptomatic children [8, 26, 27, 46, 48, 56, 61, 63]. HPVs, including 'high-risk' mucosal HPVs 16 and 18, have also been detected in tonsillar or adenoid samples from children with normal mucosa, tonsillar hyperplasia, chronic tonsillitis, or adenoid hyperplasia [9, 30, 63].

A bimodal age distribution has been observed with the highest HPV prevalence in the youngest children, with age less than 1 and adolescents, with age 13 to 20 years old [56, 61]. Caesarean delivery has been suggested as non-protective against oral HPV infection [47]. No statistically significant association has been found between the detection of HPV in the oral cavity and the gender, education, HPV-related conditions, smoking history, number of sex partners, adolescent's smoking history, or history of sexual activity [61].

The highest detection rate of HPV DNA has been found in oral swabs of newborn babies, varying from 4% to 87% [48, 64]. HPV infection in infants' buccal mucosa seems to be acquired at birth [48]. It has been proposed that newborn babies are exposed to cervical HPV infection of their mother and oral HPV infection persists for at least 6 months of age, with a decreasing rate during the first 3 years of life [8, 33, 48]. It is still unclear how frequently perinatal infection progresses to clinical lesions, whether genital, laryngeal, or oral. The concordance of HPV types detected in newborn babies and their mothers is in the range of 57% to 69% and it has been proposed that the infants might also acquire the HPV infection postnatally [33, 64].

These findings are of great importance since they demonstrate that HPV oral infection is acquired at birth as well as gradually in childhood. Oral cavity mucosa seems to be a unique reservoir of 'high-risk' mucosal HPV infection in childhood. The impact of the presence of these oncogenic HPV types in the oral cavity of children on the efficacy of vaccination against HPVs remains to be clarified.

Cervical neoplasia

Sexual activity among adolescent girls is related to high risk for developing sexually transmitted diseases including HPV infection. The prevalence rates of the HPV cervical infection in the sexual active adolescent population range

Table 2 HPV vaccines and the covered HPV types

HPV vaccines	HPV types	Adjuvants
Bivalent	16, 18	Aluminum hydroxide and monophosphoryl lipid A (AS04)
Quadrivalent	16, 18, 11, 6	Aluminum hydroxyphosphate sulfate

from 13% to 38% [35, 36]. In a recent analysis of 10,295 pediatric and adolescent Papanicolaou smears in the USA, the prevalence rate of squamous intraepithelial lesions (SILs) was 3.77%, while no cases of carcinoma were identified [36]. Interestingly, 18% of the adolescents with abnormal Papanicolaou smears had evidence of high-grade SILs. Although most low-grade SILs regress completely, the persistence of SIL and the presence of high-grade SILs in sexually active adolescents is of clinical significance as adolescents with SIL are at substantially increased relative risk of developing invasive carcinoma compared with the SIL-negative population. Although yearly Papanicolaou smear screening has been proposed for sexually active children, this recommendation is not yet included in the American Academy of Pediatrics recommendations for Preventive Pediatric Health Care [2].

HPV vaccination in childhood

The multivalent HPV vaccines are bioengineered, component vaccines made up of virus-like particles produced from the surface proteins of HPV types 16 and 18 for the bivalent and HPV 16, 18, 11, and 6 for the quadrivalent (see Table 2). Currently, both HPV vaccines have been approved by the US Food and Drug Administration as well as by the European Union. To date, several European countries have already introduced vaccination programs to girls aged 11 to 12 years [45]. Clinical trials have shown that the quadrivalent vaccine is highly immunogenic, safe, well tolerated in females 9 through 26 years of age, and its efficacy remains high for at least 5 years following vaccination [6]. Similar results have been demonstrated in the clinical trials for the bivalent vaccine.

To optimize the efficacy and thus cost effectiveness of the vaccination, it is necessary for it to be given at an age when the greatest possible proportion of vaccinated individuals has not been exposed to HPV [67]. Currently, the rationale for routine immunization at 11 to 12 years of age is that the vaccine should be given before a female becomes sexually active. In the American Academy of Pediatrics provisional recommendations, girls 11 to 12 years of age should be immunized routinely with three doses of quadrivalent HPV vaccine administered intramuscularly at 0, 2, and 6 months [13]. Both HPV vaccines are expected to offer protection against HPV 16 and 18 infection, which are responsible for more than 70% of cervical cancer cases, but not against skin warts. Additionally, the quadrivalent vaccine, which includes types HPV 11 and 6, is expected to provide protection against anogenital warts as well as RRP [17]. Since the HPV vaccine is not expected to prevent infection attributable to all high-risk HPV types, cervical cancer-screening recommendations including Papanicolaou testing should continue to be followed for patients who have received HPV vaccine. At the moment, although safety and immunogenicity studies have been completed satisfactorily for males, HPV vaccine is not recommended for boys [13]. Adolescents' access and consent to the human papillomavirus vaccine still remains a critical aspect for immunization success [16].

Conclusions

In childhood, HPV infection represents the principal cause of common warts, genital warts, RRP, and low-grade as well as high-grade SILs. Understanding the natural history of HPV infection will improve the management and treatment of HPV-infected children. Moreover, this will enable HPV vaccine studies to focus on the correct age groups and populations for vaccination against cervical cancer. In cases of children with anogenital warts, greater awareness of the natural history of HPV infection will decrease the number of lawsuits related to false allegations of sexual abuse. The role of the presence of HPV in the oral cavity of both boys and girls and its impact on HPV transmission remain to be elucidated. HPV vaccination against HPV 6 and 11 will offer protection against HPV 11/6-related anogenital warts as well as RRP in children. Both bivalent and quadrivalent HPV vaccines are expected to protect against HPV 16 and 18 infections, which are responsible for more than 70% of cervical cancer cases.

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