Review of management, treatment, and vaccination of human papilloma virus (HPV) infection in human beings.

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Abstract: The Papilomaviridae family contains sixteen genera in which human papillomaviruses (HPV) are prevalent pathogens in human beings that cause a variety of cutaneous and mucosal diseases. Common warts, genital warts, and low- and high-grade squamous intraepithelial lesions can all be caused by different HPV strains. Skin warts exists in different forms including planter warts (*Verruca plantaris*), common warts (*Verruca vulgaris*), and flat warts (*Verruca plana*). Anogenital warts are a legal and clinical issue, and evaluating minors for the risk of sexual assault should be considered in all situations. In a number of investigations, recurrent respiratory papillomatosis has also been linked to HPV infection. HPV vaccination, which was recently introduced, is predicted to prevent HPV-related cervical cancer in adults, but HPV infection will continue to impact youngsters.

Key words: Human papillomaviruses, infection, and vaccination.

Introduction

Warts are caused by infection of the epidermis with human papillomavirus (HPV). HPVs are divided into separate genotypes on the basis of their DNA sequence. Different HPV types may preferentially infect either cornified stratified squamous epithelium of skin or uncornified mucous membranes. The appearance of the lesion is influenced not only by viral type but also by environmental and host factors **(1).** Most people will experience infection with HPV at some time in their life. The prevalence of viral warts in children and adolescents in the United Kingdom has been recorded at between 39% and 49% **(2).**

More than 170 human papillomavirus (HPV) types have been sequenced, curated, and divided into five genera **(3).**Human papillomaviruses (HPVs) are little double-strandedDNA viruses that come in a variety of shapes and sizes. There are about 130 different varieties of HPVs (**4**). HPVs are divided into two types: mucosal and non-mucosal on the basis of infection sites in the skin **(5).** Mucosal types invade mucous membranes, causing cervical neoplasia in adults and anogenital warts in both children and adults.

HPV types classified as ‘high-risk' have been linked to the emergence of SILs and their progression to cervical cancer **(6).** Mucosal HPV types 16 and 18 are the most common "high-risk" kinds found in the female urogenital system, and they are found in more than 70% of women with cervical cancer **(7).** Mucosal HPVs of both ‘ high-risk ' and ‘ low-risk ' types have been implicated in the formation of SILs, with ‘ low-risk ' types 6 and 11 accounting for about 90% of genital wart instances **(6,7).** Cutaneous forms infect the skin's squamous epithelium, resulting in common warts, plantar warts, and flat warts on the hands, feet, and face. Epidermodysplasia verruciformis, a rare familial disorder associated with the development of large cutaneous warts that can progress to skin cancer **(8)**, and WHIM syndrome, a rare combined immunodeficiency syndrome characterised by warts, hypogammaglobulinemia, and myeloka-

thexis and recurrent bacteriuria, have specific cutaneoustypes (**9).** Despite the fact that HPV infection is mostly spread through sexual contact, it can also be transferred through non-sexual routes such as casual physical contact and prenatal vertical transmission **(10,11)**. Through abrasion of the skin or mucosa, the virus infects predominantly epithelial cells, where it can live as a long-term latent infection that can reawaken or persist **(11).** HPV infection is temporary and asymptomatic in the majority of people, and most occurrences of HPV infection resolve within two years **(12).** The progression of HPV infection is known to be influenced by a number of variables. Individual susceptibility, immune status and nutrition, endogenous and exogenous hormones, tobacco 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, viralload, HPV variant, and viral integration are all factors to consider **(12,13).**

Genital and anal warts

Sexual intercourse is most prevalent factor responsible for genital warts. Anogenital warts in children are uncommon, considerably less in adults; yet, the reported frequency of pre-pubertal children has been steadily increasing since 1990 (**14)**. Anogenital warts can appear in the vulvar, vaginal, urethral, and peri-anal areas in girls. In boys, genital warts are most commonly found in the peri-anal area, with penile warts being uncommon. Anogenital warts are three times as common in girls than in boys **(15).** Anogenital warts can range in appearance from small, skin-colored flat warts to moist, pink to brown lesions located in the skin creases and around the vaginal and anal openings **(16).** The most common HPVs found in anogenital warts in children are HPV11 **(14, 17).** Cutaneous HPV types such as HPV2 or 3 are also seen, but their prevalence is minimal (**17**). Skin kinds 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 areas among non-sexually abused children with anogenital warts (**17**). Mucosal forms, on the other hand, are more common in girls, children under the age of three, children with relatives who have genital warts, and those who have no warts elsewhere (**17**). HPV genital transmission routes in children are still debated. HPV can be transmitted vertically or through intimate touch, which can be sexual or non-sexual, to a child's anogenital area (**18**, **19**). Several researchers have suggested that sexual interaction is the most common method of HPV transmission in children (**18**, **19**). In a study by Stevens-Simon *et al.* it was discovered that genital HPV infection was more common in sexually abused girls than non-sexually abused girls, and that the majority of them remained asymptomatic (**20**). Recent research suggests that, while sexual contact is a probable route of HPV transmission, alternative routes such as perinatal transmission, autoinoculation and heteroinoculation, and possibly indirect transmission via fomites are more common (**11**,**21**). The rate of anogenital warts in non-abused children was found to be comparable to the rate reported in abused children (**22**). Intriguingly, 'high-risk' HPVs have been found in 4–15 percent of genital samples acquired from asymptomatic neonates, with genital HPV DNA carriage decreasing over the first year of life (**23**). HPV appears to be frequent in asymptomatic prepubescent girls who have no documented vulvar infection.

Management

Anogenital warts in minors, however, have important social and legal ramifications since they raise concerns about suspected sexual abuse (**18,24,25**). As a mechanism of acquisition, the likelihood of sexual abuse increases with age in childhood (**10, 21).** Sexual assault is less likely to be implicated in cases of

children with anogenital warts below a certain age **(21**). Every case must be thoroughly examined in order to decide whether there is sufficient cause for further investigation. If the infection was not acquired prenatally, it has been suggested that anogenital warts in children indicate maltreatment; however, the timeframe for perinatal transmission has not been defined (**10**). The most typical upper age limits for perinatal transmission are 12 to 24 months, and anogenital warts found in children older than 24 months are frequently thought to have been acquired by sexual assault. All children who come with anogenital warts should be reviewed by a child sexual abuse expert, and children over the age of four should be referred to Child Protection Services on a regular basis (**10**). Children with anogenital warts should be treated using a multidisciplinary approach in these circumstances (**19**). Because of HPV's long latency and the possibility of vertical and non-sexual transmission, it has been suggested that obtaining a history, assessing the socio-clinical environment, and performing a physical examination are the best ways to discover suspected sexual abuse (**26**). The clinical appearance of the lesions or human papillomavirus type cannot be used to determine the mode of transmission of anogenital warts in children. The majority of occurrences of anogenital warts in children are most likely the consequence of non-sexual transfer, specifically prenatal transmission. As a result, unless there are other causes for suspicion, these patients should be treated differently (**27**).

Anogenital warts in children spontaneously resolve in more than half of cases, and non-intervention has been advised as a fair first management approach (**15**). Although there are no longitudinal studies available to determine if children with anogenital warts are at risk of acquiring cancer in young adulthood, long-term follow-up is advised (**28**).

Skin warts

The major manifestation of the cutaneous HPV types is skin warts, with HPV 1, 2, 3, 4, 27, and 57 being the most often diagnosed (**29,30**). Although cutaneous HPV types are most commonly found in skin warts, mucosal HPVs have also been found; nevertheless, the origin and significance of these kinds on the skin are unknown (**29,30,31**). Common warts (*Verruca vulgaris*), plantar warts (*Verruca plantaris*), and flat warts (*Verruca plana*) are all types of skin warts. Skin warts are thought to affect up to 10% of children and young adults, with the highest frequency occurring between the ages of 12 and 16 (**30**). Warts are more common in girls than in boys. Common warts account for 70% of skin warts and are most common in children, but plantar and flat warts are more common in adults (**42)**. HPV infection of normal skin is thought to be acquired relatively early in childhood (**32**). In most cases, cutaneous HPV types cause persistent subclinical infections in healthy people without developing warts or other skin lesions (**33**). In 40 percent of children, warts spontaneously vanish after two years without treatment, according to the natural course of cutaneous warts in childhood. Warts can be painful depending on where they are located, such as in the soles of the feet or near the nails, or they might be considered as socially unacceptable when they are found on visible places, such as the hands or face (**34**).

Management

There are numerous approaches to wart therapy available today, as no single therapy has been shown to be effective in reaching complete remission in every patient (**35, 36).** Salicylic acid, cryotherapy, laser therapy, imiquimod, bleomycin, retinoids, and immunotherapy are examples of these. The distribution, size, and number of lesions, the child's age, previous therapies, the child's and parents' capacity to tolerate and follow treatment recommendations, concomitant conditions, and potential adverse effects should all be considered before choosing a treatment **(37).**

Homeopathy and wart treatment

Homoeopathic remedies for warts can be found in the homoeopathic repertory which prescribes Calcarea carbonica, Causticum, Dulcamara, Natrum muriaticum, Nitric acidum, Thuja occidentalis, and more as homoeopathic remedies (**38**).

- Calcarea carbonica: Calcarea carbonica is indicated in warts which may be fleshy, horny, painful, and offensive. Patient is usually chilly, lazy and indolent, and fearsome
- Causticum: Causticum is indicated in old, pedunculated warts, suppurating with great sensitivity to touch. Hard, horny warts that bleed easily. Deep burns and their effects. Patient is sympathetic and anxious
- Dulcamara: Dulcamara is indicated in flat and hard warts located on backs of hands and face. Also indicated in Homeopathic management of large warts. Patient is worse in cold, damp weather, or humidity
- Natrum muriaticum: Warts on palms and fingers. Patient is sensitive, sentimental, reserved, and resentful. They also have marked craving for salt
- Nitric acidum: Nitric acidum is large, fissured warts that itch and sting or bleed upon washing. This remedy is also indicated for people who are anxious about health and worry about cancer. Often useful for warts that have a horny wall surrounding a central depression or the more common plantar wart
- *Thuja occidentalis:* The most common homeopathic remedy for various kinds of warts. *Thuja* is indicated in isolated, jagged warts that smell or bleed easily or mosaic warts on the sole of the foot. It is commonly needed for genital warts

Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is the most frequent benign tumor of the larynx in children, with an incidence ranging from 0.3 to 3.9 per 100,000 **(15, 68).** Recurrent growth of benign papillomas along the epithelium of the upper respiratory tract, including the larynx, vocal cords, thearytenoids, subglottis, and trachea, characterizes this condition. The mucocutaneous edge of the genuine vocal cords, where the squamous epithelium of the vocal cord meets the respiratory epithelium of the larynx, is the most usually afflicted location. Exolaryngeal areas such as the lungs, oropharynx, oral cavity, and nasal cavity may be affected. RRP is a potentially life-threatening benign tumor that grows in size and number, obstructing the airway completely (**39**). Hoarseness, varying degrees of persistent dyspnea, cough, stridor, dysphonia, or a faint cry are the most prevalent presenting symptoms in children with RRP (**40,41**). Symptoms might last anywhere from two months to more than two years until a conclusive diagnosis is made. Early RRP symptoms include hoarseness, weak cry, and aphonia, as well as voice disruption with or without stridor. The beginning of symptoms can occur at any age between birth and six years old. When other common paediatric airway illnesses fail to follow the natural history or do not respond to treatment, RRP should be explored. Direct laryngoscopy and tissue biopsy are used to confirm the diagnosis of RRP.

The infection of the upper airway with HPV types 6 and 11 is the cause of RRP (**17**). Because HPV infection is almost always the result of prenatal transmission, sexual abuse isn't a factor in RRP cases (**33**). Perinatal infection can spread through the placenta, through amniotic fluid during pregnancy and delivery, and through direct contact with cervical and genital lesions during birth. RRP rates are higher in firstborn children and those born vaginally than with subsequent children or those born via Caesarian section (**42**). Higher incidence of RRP in children are also linked to maternal history of anogenital warts, cytological or histological lesions of HPV infection in the genital tract, and maternal age less than 20 years (**42**).

However, how often prenatal infection leads to clinical lesions, whether vaginal, laryngeal, or oral, is unknown. RRP is characterized by a low viral load of HPV (**43**). In most children with recurrent respiratory papillomatosis, viral levels of HPV 6 and HPV 11 remain rather steady throughout time (**44**). RRP is thought to be caused most commonly by HPV 11 (**45**). Children with RRP infected with HPV 11 are more likely to develop severe illness and require more surgical intervention than children with HPV 6 (**43**). Infection with HPV 11 is also linked to the requirement for adjuvant therapy, tracheal and pulmonary illness, and tracheostomy (**45**).

Management

RRP is treated with surgical removal depending on the degree of airway involvement, with significant recurrence rates after therapy (**46**). Surgical excision of RRP in children is done with a variety of lasers, including CO2, KTP, and pulsed dye (**47**). Adjuvant pharmacologic medicinal therapy, such as cidofovir or interferon, may also be used (**40**). Affected children typically require many interventions, which have a significant impact on patients, their families, and the healthcare system, with an estimated yearly cost of 109 million dollars in the United States (**39**). Surgical debulking techniques typically result in long-term dysphonia, laryngeal scarring, and, in rare cases, malignant degeneration (**48**). Inter-surgeon variability, the size and severity of papillomas at the time of laryngoscopy, and the use of adjuvant medicinal therapy are all factors that influence the temporal course of RRP (**40**). To date, several studies have used oral swabs or washings from healthy asymptomatic children to demonstrate the presence of HPV DNA in the children's buccal cavity (**23**,**44**). HPVs have been found in tonsillar or adenoid samples from children with normal mucosa, tonsillar hyperplasia, chronic tonsillitis, or adenoid hyperplasia (**49**). A bimodal age distribution has been reported, with the highest HPV prevalence among infants and children under the age of one, as well as adolescents aged 13 to 20 years old (**50**). Caesarean section has been shown to be non-protective against HPV infection in the mouth (**51**). There is no statistically significant link between HPV detection in the oral cavity and gender, education, HPV-related diseases, smoking history, number of sex partners, teenage smoking history, or sexual activity history (**51**). Oral swabs of newborn newborns have the greatest detection rate of HPV DNA, ranging from 4 percent to 87 percent (**23**). HPV infection of the buccal mucosa in neonates appears to be acquired at birth (**23**). It has been shown that newborn babies are exposed to their mother's cervical HPV infection, and that oral HPV infection lasts at least 6 months, with a decreasing rate over the first three years of life (**53**). It's uncertain how often prenatal infection leads to clinical lesions, such as genital, laryngeal, or oral lesions. The concordance of HPV types discovered in newborn and their mothers ranges from 57 to 69 percent, and it has been suggested that the infants may acquire HPV infection postnatally (**54**). These findings are significant because they show that HPV oral infection can occur at birth as well as later in childhood. In childhood, the mucosa of the oral cavity appears to constitute a unique reservoir of ‘high-risk' mucosal HPV infection. The influence of the presence of these oncogenic HPV strains in children's oral cavity on the efficiency of HPV vaccination is still unknown.

Cervical neoplasia

Adolescent girls who engage in sexual activity are at a higher risk of contracting sexually transmitted illnesses, such as HPV infection. In the sexually active adolescent population, HPV cervical infection prevalence rates range from 13 percent to 38 percent (**55**,**56**). The prevalence rate of squamous intraepithelial lesions (SILs) was 3.77 percent in a recent study of 10,295 paediatric and adolescent

Papanicolaou smears in the United States, with no cases of cancer found (**56**). Surprisingly, high-grade SILs were found in 18% of the teenagers with abnormal Papanicolaou smears. Although most low-grade SILs resolve completely, the persistence of SIL and the existence of high-grade SILs in sexually active teenagers is clinically significant because adolescents with SIL have a significantly higher relative risk of acquiring invasive cancer than those who do not have SIL. Although yearly Papanicolaous smear screening for sexually active children has been advocated, it is not yet included in the American Academy of Pediatrics Preventive Pediatric Health Care recommendations (**57**).

Vaccination

Vaccines form an important part of management strategy. Multivalent HPV vaccinations are bioengineered which are comprised of virus-like particles synthesized from the surface proteins of HPV types 16 and 18 for bivalent vaccines and HPV 16, 18, 11, and 6 for quadrivalent vaccines. The US Food and Drug Administration, as well as the European Union, have approved both HPV vaccines at this time. Vaccination programs for girls aged 11 to 12 years have previously been implemented in a number of European nations. (**58**). Clinical trials have demonstrated that the quadrivalent vaccine is highly immunogenic, safe, and well tolerated in females aged 9 to 26, and that its efficacy lasts at least 5 years after vaccination (**59**). In the clinical trials for the bivalent vaccine, similar effects were seen. To maximize the vaccination's efficiency and consequently cost effectiveness, it must be administered at a time when the maximum feasible proportion of vaccinated individuals has not been exposed to HPV (**60**). The vaccine should be given before a girl becomes sexually active, according to the current rationale for routine immunization at 11 to 12 years of age. According to the provisional guidelines of the American Academy of Pediatrics, girls aged 11 to 12 years should be routinely inoculated with three doses of quadrivalent HPV vaccination delivered intramuscularly at 0, 2, and 6 months (**61**). Both HPV vaccines are likely to protect against HPV 16 and 18, which cause more than 70% of cervical cancer cases, but not against skin warts. Furthermore, the quadrivalent vaccine, which includes HPV types 11 and 6, is predicted to protect against anogenital warts and RRP (**62**). Because the HPV vaccine is not predicted to prevent infection caused by all high-risk HPV types, individuals who have received the vaccine should continue to follow cervical cancer screening recommendations, including Papanicolaou testing. HPV vaccine is currently not recommended for boys (**61**), despite the fact that safety and immunogenicity studies for guys have been completed adequately. The availability and permission of adolescents to receive the human papillomavirus vaccination is still a critical factor in immunisation success (**63**).

Conclusion

There are numerous approaches to wart therapy available today, as no single therapy has been shown to be effective in reaching complete remission in every patient. HPV infection is the leading cause of common warts, genital warts, RRP, and low-grade and high-grade SILs in children. Understanding the natural history of HPV infection can help doctors better manage and treat HPV-infected kids. Furthermore, this will allow HPV vaccine studies to focus on the appropriate age ranges and demographics for cervical cancer vaccination. Greater awareness of the natural course of HPV infection will reduce the frequency of lawsuits connected to false allegations of sexual abuse in cases of children with anogenital warts. The role of HPV in the oral cavity of both boys and girls, as well as its impact on HPV transmission, is yet unknown. In youngsters, HPV vaccination against HPV 6 and 11 will protect them from HPV11/6-related anogenital warts as well as RRP. HPV 16 and 18 infections, which account for more

than 70% of cervical cancer cases, are likely to be protected by both bivalent and quadrivalent HPV vaccines.

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