

Mucocutaneous warts in children: clinical presentations, risk factors, and response to treatment

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Abstract

Introduction: Human papillomaviruses (HPV) cause cutaneous and mucosal infections in both adults and children. Warts are very common in children.

Methods: All patients younger than 13 presenting with cutaneous warts in a 1-year period at Farwaniya Hospital in Kuwait were included in the study. In addition, their parents completed a questionnaire about possible environmental risk factors for warts. The treatment modalities used and their outcomes were recorded.

Results: This study included 2,916 children with warts. Common warts affected male patients more frequently. Warts were mostly located on the hands, in 1,172 patients (40.19%), followed by the feet in 1,096 patients (37.59%). Frequently associated environmental factors were walking barefoot, using a swimming pool, or having a family member with warts. The first-line treatment used was cryotherapy, followed by topical salicylic acid preparations. A total of 2,128 (72.98%) patients were cleared of their warts, and 232 (10.90%) patients had a recurrence. The cure rate in patients with hand warts was slightly higher than with warts on the feet (78.67% versus 70.52%). Treatment side effects were a complaint of 1,796 (61.59%) patients.

Conclusions: The prevalence of warts is lowest among children less than 6 years old. No particular therapy has been confirmed to be effective at achieving complete remission in every patient.

Received: 24 November 2012 | Returned for modification: 5 February 2013 | Accepted: 13 February 2013

Introduction

Human papillomaviruses (HPVs) are small DNA viruses of the papillomavirus family. As of May 2010, at least 189 distinct PV types had been described, of which 151 were found in humans on the basis of viral DNA analysis (1). HPVs are among the most common infectious agents in humans and they present with a wide variety of cutaneous manifestations, ranging from benign proliferative warts to carcinomas.

The classification of warts into mucosal and cutaneous types depends mainly on their morphological features and anatomical localization (2). HPVs are associated with numerous skin manifestations, including common warts (*verruca vulgaris*), plantar warts, plane warts (*verruca plana*), anogenital warts, and those associated with epidermodysplasia verruciformis (EV) (3).

Verrucae are spread by direct skin-to-skin contact or indirectly via contact with contaminated surfaces (e.g., swimming pools or communal showers) (4). Having a family member with a wart has been shown to be stronger risk factor to the child than the use of swimming pools and shared bathing areas (5). Laboratory diagnosis of skin warts is usually unnecessary because they can be distinguished morphologically (6). Currently available treatment options are lengthy, expensive, inconvenient, and often painful. The recurrence rate is very high because of the persistence of the virus in adjoining normal skin (7).

Warts may be associated with significant psychological stress in patients with confluent lesions present on cosmetically important areas such as the face and hands.

The aim of this study was to study the epidemiology and prevalence of mucocutaneous warts in children under 13 in Kuwait, and to assess the clinical effectiveness and tolerability of various treatment modalities.

Patients and Methods

This study was performed at the outpatient dermatology clinic of Al-Farwaniya Hospital, Kuwait during the period from February 2011 to February 2012 on all patients younger than 13 that presented with cutaneous manifestation of HPV infection as common and/or plantar warts.

Demographic data including patients' age and sex, and the duration, location, size, and number of lesions were recorded on standard forms with schematic representation of the body parts. Informed consent was obtained from parents for their children, and they were asked to complete a questionnaire about possible environmental risk factors, including a family member with wart(s), whether the mother had genital warts at the time of delivery, walking barefoot at home and during sports, and the use of public swimming pools.

The treatment modalities used and their outcomes were recorded. The number of warts were counted prior to treatment and at each subsequent visit. No improvement was defined as warts that did not decrease in number or size or worsened with treatment. Improvement was defined as a reduction in the number of warts and/or size of warts. A wart was considered cured if it was no longer seen and could no longer be felt. We recorded the occurrence of any post-treatment side effects such as blistering, pain, or erosion.

Results

A total of 2,916 children (1,712 males and 1,204 females) younger than 13 with clinical presentation of warts were included in this study. The age range was from 8 months to 12 years. The most frequently affected children were between 8 and 10 years old; see

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Table 1 | Cutaneous HPV infection, relative prevalence by gender and age. CW – cases with common warts, PW – cases with plane warts, AGW – cases with warts in the anogenital area.

Age (years)	Male				Female			
	CW (%)	PW (%)	AGW (%)	Total (%)	CW (%)	PW (%)	AGW (%)	Total (%)
0-2	20 (1.17)	0	0	20 (1.17)	32 (2.67)	0	4 (0.33)	36 (2.99)
2-4	84 (4.91)	0	12 (0.70)	96 (5.61)	52 (4.32)	4 (0.66)	4 (0.33)	60 (4.98)
4-6	216 (12.62)	4 (0.23)	24 (1.40)	244 (14.25)	180 (14.95)	0	8(0.66)	188 (15.61)
6-8	310 (18.11)	12 (0.70)	18 (1.05)	340 (19.86)	220 (18.27)	0	24 (1.99)	244 (20.27)
8-10	500 (29.21)	8 (0.47)	24 (1.40)	532 (31.07)	348 (28.90)	0	20 (1.66)	368 (30.56)
10-12	472 (27.57)	8 (0.47)	0	240 (28.04)	264 (21.93)	12 (3.32)	32 (2.67)	308 (25.58)
Total	1602 (93.57)	32 (1.87)	78 (4.56)	1,712	1,096 (91.03)	16 (1.33)	92 (7.64)	1,204

Table 1. Common warts affected boys more frequently than girls in all age groups.

The duration of warts ranged from 1 week to 2 years. The mean number of warts per patient was 5.6 warts. The hand had the highest mean number of warts (mean = 7 warts) with a predominance around the fingers (mean = 5 warts).

Warts were present most frequently on the hands, in 1,172 patients (40.19%), followed closely by warts on the feet in 1,096 patients (37.59%). Multi-site wart infections were experienced by 252 male and 104 female patients, mostly on their hands, feet, and genitalia. Figure 1 shows the distribution of warts according to sites of involvement. Warts in the anogenital area were present in 170 (5.83%) children. The youngest patient was an 8-month-old girl with perianal warts.

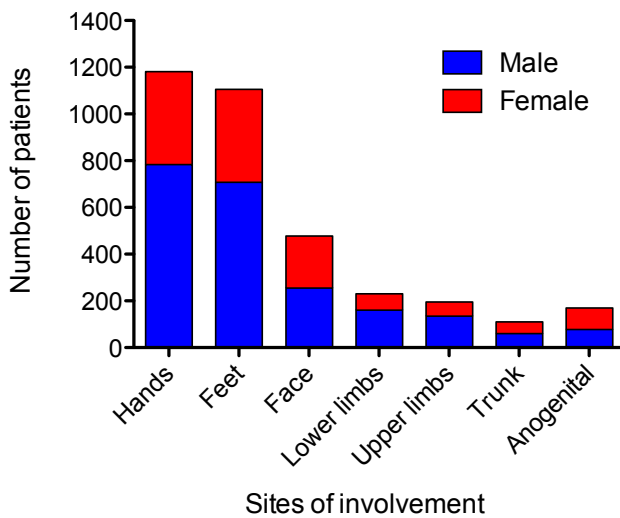


Figure 1 | Sites of Involvement of warts in male and female children.

The prevalence ratio between common and plane warts was 59.4:1; see Table 1. Plane warts showed highest prevalence in the 6- to 8-year-old range in males, and in the 10- to 12-year-old range in females. A comparison of the prevalence of plane warts in children in the lower age group (0-6 years) with children in the higher age group (6-12 years) showed a sevenfold increase in males and a threefold increase in females.

The results of the parent survey on possible positive environmental risk factors for warts are summarized in Table 2. The use of public swimming pools showed a significantly increased risk of getting warts. In addition, children with a close family member or house maid (or other servants) with warts had an increased risk of infection.

The outcome of various treatment modalities was recorded and is shown in Figure 2. The first-line treatment in this study was cryotherapy (with an interval of 2 weeks between treat-

ments), followed by patient self-application of topical salicylic acid preparations. A total of 2,128 (72.98%) patients were cleared of their warts; but the treatment failed to work for 788 (27.02%). In addition, in 232 patients (10.90%) the warts recurred, and the mean time of recurrence was 5.9 months (range 3-8 months).The response rate (improvement) to any treatment used was higher for small warts than large ones, but the difference was not statistically significant (91.42% versus 87.68%), whereas there was no significant correlation between the size of the wart and the number of treatment sessions required to clear it. There was no difference in the cure rate for the different age groups. The cure rate in patients with hand warts was slightly higher than that of warts on the foot (78.67% versus 70.52%). Many warts, especially planar warts, required treatment with a combination of cryotherapy and salicylic acid therapy. The average number of treatments for cured patients was 3.7 (range 1-8).

Of the 2,916 treated patients, 1,792 (61.45%) complained of complications such as blistering (7.41%), stinging or tenderness (6.45%), erosion (9.47%), erythema (13.72%), and hyperpigmentation (1.97%), as shown in Table 3. A total of 680 (23.32%) patients suffered from a mixed combination of the above side effects. Clinically, the patients that were treated using a combination of cryotherapy and salicylic acid showed more complications (82.24%).

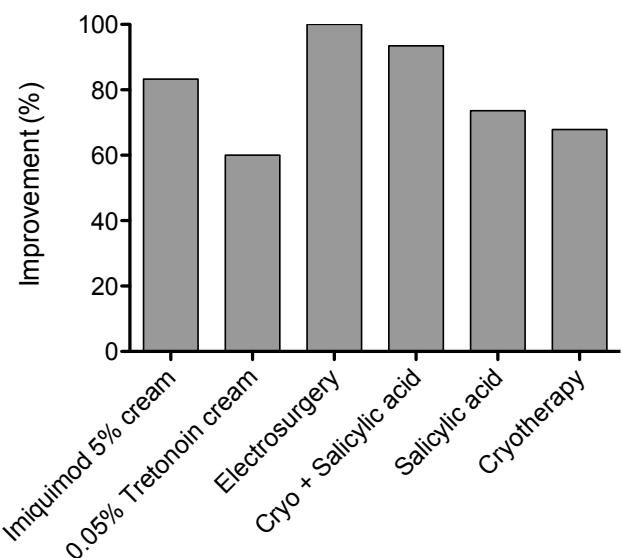


Figure 2 | Improvement (%) observed with different treatment modalities.

Discussion

HPVs are tiny non-enveloped, double-stranded DNA viruses capable of infecting mucosal or cutaneous epithelium, thus inducing cutaneous and mucosal proliferation of epithelial cells clinically

Table 2 | Incidence of potential environmental risk factors in children with warts.

Potential risk factor Age (years)	Number of positive responses
Family member with wart(s)	580
Mother with genital warts at time of delivery	4
Walking barefoot at home	1,548
Use of public swimming pools	1,644
Walking barefoot during sports	176

characterized as papillomas, condylomas, and warts (8). These viruses can remain latent for long period of time and reactivate later, or persist actively without being clinically visible. The HPV virus is capable of surviving in the environment for many months and at low temperatures. Therefore an individual with plantar warts can spread the virus by walking barefoot.

The main HPV types infecting the skin are distributed over five genera (alpha, beta, gamma, mu, and nu) and 16 species (8). The HPV types most frequently detected in warts belong to species of three genera (alpha, gamma, and mu). The specific types of HPVs that cause common and flat skin warts are from the alpha (e.g., HPV2 and HPV3), gamma (e.g., HPV4), mu (HPV1 and HPV63), and nu (HPV41) genera (11). The incidence of common warts (*verruca vulgaris*) in children is estimated at up to 33% (5). A survey of 10,000 pediatric dermatology patients in Kuwait showed viral warts to be the second most prevalent dermatosis, involving 13.1% of patients (12).

Comparing the frequencies of specific skin site involvement in both sexes at all ages, we found hand involvement to be higher in males, as reported by Theng et al. (13). This may be attributed to boys being physically more active in comparison to girls, making them at higher risk of trauma to the stratum corneum, which serves as an entry point for the virus (13). However, the overall prevalence of warts in both sexes was comparable (93.57% in the male group and 91.03% in the female group for common warts; 1.87% in the male group and 1.33% in the female group for plane warts; and 4.56% in the male group and 7.64% in the female group for genital warts), as shown in earlier studies (14, 15).

We noted the peak prevalence of warts in the 8- to 10-year-old group. Comparing the prevalence of plane warts in children in different age groups, our results (Table 1) showed that HPV infection was higher in the age groups above age six, with a sevenfold and a threefold increase in males and females, respectively. Our results were in line with an Australian study (16) that showed the highest prevalence of warts in school-age children.

Data analysis of the questionnaire completed by the parents revealed that the environmental risk factors most commonly associated with warts in their children were the use of public swimming pools, followed by walking barefoot. The findings were more or less similar to those reported in some past studies (4, 17, 18). This indicates that not wearing shoes—as seen in both these activities—leads to transmission of virus. The third common environmental risk factor was the presence of warts in a family member. A British study (5) carried out among primary school children

showed that having a family member with a wart was a stronger risk factor for the child than using swimming pools and shared bathing areas. Transmission within families and schoolmates probably plays an important role. Hence, primary school children with a family member with warts or classmates with warts have a higher risk of getting the infection. This was substantiated in a study that showed that the 26 to 32% of HPV-positive children shared at least one common HPV type with their parents at some point in time (19). Although genital warts in children should be taken as a sign of child abuse and necessitate a sexual abuse assessment, frequently such lesions results from virus inoculation through nonsexual contact such as perinatal transmission, auto-inoculation (by scratching) from one site of the body to another, hetero-inoculation from other family members, and indirect transmission via fomites. Of the 170 children suffering from warts in the anogenital area, 66 (38.82%) of them had concurrent common hand warts, possibly leading to autoinoculation from their hand warts, as suggested by Sonnex et al. (20), who detected the same HPV type from both genital and finger samples in 27% of patients. Autoinoculation of HPV also explains dissemination of the lesions to different body sites (21). Twenty-eight of our patients' mothers had concurrent common wart infections, and another 62 children were in contact with wart-infected housekeepers and maidservants taking care of them. Our study suggests that hand-genital transmission may occur from warts on patients' own hands or on the hands of a caretaker or family member, in agreement with the study by Fairley et al. (22).

A single most effective treatment for warts that achieves a complete cure in every patient is still elusive (23), and thus different types of combination treatments have been used to achieve higher cure rates. We used different treatment modalities to treat warts in our patients based on the type and site of warts, as suggested in an earlier study (24). The two most common treatments used have been patient-applied salicylic acid and physician-administered cryotherapy with liquid nitrogen (25). Among the various treatment modalities used in our study, cryotherapy was our first choice of treatment, and was applied at 2-week intervals using a sustained 10-second freeze, followed by salicylic acid application and cryotherapy / salicylic acid combination therapy. The cure rate in our patients using cryotherapy was 67.86%. Cure rates in some other studies have ranged from 39% to 75.7% (26, 27).

Cryotherapy is able to directly destroy the viral-affected keratinocytes (28), and can also elicit the immunologic response causing secondary cell damage (29). In a head-to-head trial of salicylic acid compared with cryotherapy, it was found that cryotherapy was significantly better than salicylic acid for treating hand warts, but there was no significant benefit of cryotherapy compared to salicylic acid in plantar warts (26). Salicylic acid used as monotherapy has been shown to produce clearance in 67% of patients with hand warts and 84% in those with plantar warts in 12 weeks (30).

The response to salicylic acid treatment in our study was

Table 3 | Side-effects of various treatment modalities observed during the study period.

	Cryotherapy	Salicylic acid	Cryotherapy and salicylic acid combination	Electrosurgery	Topical retinoids	Imiquimod	Total
Erythema	256 (12.72%)	44 (12.09%)	72 (16.82%)	4 (6.25%)	12 (42.86%)	12 (60.00%)	400 (13.72%)
Blistering	176 (8.75%)	0	28 (6.54%)	12 (18.75%)	0	0	216 (7.41%)
Erosion	84 (4.17%)	92 (25.27%)	100 (23.36%)	0	0	0	276 (9.47%)
Stinging or tenderness	36 (1.79%)	68 (18.68%)	60 (14.19%)	8 (12.50%)	12 (42.86%)	4 (20.00%)	188 (6.45%)
Hyperpigmentation	24 (1.19%)	0	8 (1.87%)	0	0	0	32 (1.97%)
Mixed side effects	584 (29.03%)	0	84 (19.63%)	12 (18.75%)	0	0	680 (23.32%)
Total	1,160 (27.88%)	204 (56.04%)	352 (82.24%)	36 (56.25%)	24 (85.71%)	16 (80.00%)	1,792 (61.45%)

73.63%. The response was higher compared to cryotherapy (67.86%), with an odds ratio of 0.7609 and p value of 0.1318, which is not statistically significant. A combination of physician-applied cryotherapy and patient-applied topical salicylic acid achieved high cure rates (93.46%) with an odds ratio of 5.1173 ($p < 0.0001$) when compared to cryotherapy alone, and an odds ratio of 6.6251 ($p < 0.0001$) when compared to salicylic acid alone, which is statistically highly significant. Hence the combination of cryotherapy and topical salicylic acid application is significantly effective in treating warts, but was associated with high rates (82.24%) of local side effects, especially erosions (23.36%) and erythema (16.82%), as well as blistering, stinging, and tenderness.

We used topical retinoids for treatment of flat warts and small common warts on the face. The cure rate was low (40.00%). Brodell et al. (31) reviewed several case studies and recommended oral and topical retinoids as a second-line therapy for the treatment of plane warts.

Imiquimod 5% cream was introduced for the treatment of anogenital warts in 1997 (32). This drug is the first approved topically active Toll-like receptor (TLR) 7 agonist, which activates innate immune cells to produce various cytokines including interferon- α . The induced cytokine cascade, in combination with enhanced antigen presentation, promotes an antigen-specific Th-1 cell-mediated immune response (33). We treated 48 patients with genital warts with Imiquimod applied topically 3 days a week at bedtime, followed by 4 days of rest. Imiquimod treatment achieved a cure

rate of 83.33% in our study. Schöfer et al. (34) stated that, in the treatment of anogenital warts, imiquimod 5% cream alone or in combination with ablation was superior to ablation alone in reducing the recurrence.

All therapies were associated with local skin reactions including erythema, blistering, erosions, pain, and skin pigmentation. Erythema and erosions were the two most frequent adverse events found in our patients. Cryotherapy had the lowest (27.88%) incidence of side-effects, whereas topical retinoids had the highest (85.71%) incidence of side-effects. Treating with topical retinoids (85.71%), cryotherapy and salicylic acid combination (82.24%), and imiquimod cream (80%) led to at least 80% of patients suffering from some form of side-effect, hence it is necessary to be on guard when using these treatments.

Conclusion

The prevalence of warts is lowest among children under age six. The most common types of cutaneous warts are common warts, with the hands being the most frequent site involved. No particular therapy has been confirmed to be effective at achieving complete remission in every patient. As a result, different approaches to wart therapy exist. Numerous variables influence the choice of a treatment, such as the size, number, and location of the warts. All treatments can cause local side effects, and patient tolerability may influence treatment selection.

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