

Comparison of the risk factors and HPV types in males with anogenital warts with and without involvement of the urethral meatus in western Iran

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Abstract

Background: Human papillomavirus (HPV)-induced lesions rarely develop in the urethral meatus (UM); however, their eradication can be problematic.

Methods: A total of 22 patients with anogenital warts (AGWs) in the UM region and 22 patients with AGWs located at other anatomical sites were included in this cross-sectional study. The presence of human papillomavirus (HPV) types in biopsy samples was determined using the HPV Easy typing kit (GenID GmbH, Germany).

Results: Although the patients in the AGW group with involvement of the UM had a higher incidence of reported multiple sexual partners (63.6% vs. 40.9%), larger meatus size (81.8% vs. 36.4%), and more frequent anal (36.4% vs. 18.2%) or unprotected sexual contact (68.2% vs. 36.4%) than those in the AGW group without UM involvement, only the duration of lesions ($p = 0.04$) and meatus size ($p = 0.004$) were significantly different in both groups. Low-risk HPV types were found in 75.0% and 69.2% of patients in the AGW groups with and without UM involvement, respectively.

Conclusion: We found that a larger UM size was more prone to the development of meatus AGWs; however, being married, delaying sexual debut, and avoidance of multiple sexual partners seemed to be associated with a decreased risk of development of AGWs, especially within the UM region.

Keywords: sexually transmitted infections, urethral meatus warts, HPV typing, prevention

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Introduction

Anogenital warts (AGWs) are the most common sexually transmitted infections (STIs) (1–3). There are several risk factors for the development of AGWs in men, including sexual contact at a younger age, having multiple sexual partners, being uncircumcised, and having unprotected sexual contact, as well as smoking, low socioeconomic status, and poor education (4, 5).

HPV-induced lesions rarely develop in the urethral meatus (UM) and are prone to unsuccessful treatment because of a difficult approach, limitations in safe optional treatment, and fear of complications, especially urethral stenosis. There are few reports regarding susceptibility to the development of AGWs in the UM, in which most of the patients are in their third decade and usually have a previous history of STIs. Urethral instrumentation is also a risk factor, especially in older men, while AGWs with UM involvement are rarely associated with urethral malformations such as hypospadias (6–9).

Because of the increasing incidence of genital HPV infections, the UM being an unusual site for AGWs, the difficulty of eradicating AGWs in this region, and a lack of studies regarding the risk factors of AGWs in the UM, we compared the risk factors and HPV types in males with AGWs with and without UM involvement.

Materials and methods

Study population

This cross-sectional study was carried out on 22 heterosexual men

with AGWs with involvement of the UM and 22 heterosexual men with AGWs without involvement of the UM at the Hajdaie Dermatology Clinic in Kermanshah, Iran, over a period of 3 years (2013–2016). Patients whose AGWs with or without involvement of the UM were documented clinically or through histopathological assessment were included in the study. Patients with immunodeficiency, urethral anomaly, recent catheter insertion, or psychological problems, and those that were uncircumcised were excluded from the study.

Demographic data, marital status, sexual habits, number of sexual partners, duration of the disease, and other concurrent STIs were recorded in a questionnaire.

Written informed consent was obtained from every patient. The study was approved by the ethical committee of Kermanshah University of Medical Sciences; the information for all of patients was kept confidential.

Measurement of urethral meatus size

Assessment of UM size was carried out following appropriate UM treatment and its improvement nearly 1 month after treatment. For measurement of UM size, we used a Nelaton urinary catheter with variable sizes. In patients for whom the Nelaton urinary catheter was easily inserted, a Nelaton urinary catheter equal to or smaller than 18 French (each French is equivalent to 1/3 millimeter) was regarded as a small size, but larger than 18 French was considered a large size for the UM.

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Diagnosis of AGWs and other STIs

In typical clinical presentations, the diagnosis was based on clinical findings, but if there was any doubt in clinical diagnosis then appropriate laboratory assessments such as histopathological or microbiological evaluations were carried out.

Detection and differentiation of HPV types

Tissue samples of AGWs were collected with a shave biopsy, fixed in 10% formalin, and subjected to HPV type microarray detection by PCR and subsequent reverse dot-blot hybridization with sequence-specific oligonucleotide probes. We used an HPV Easy typing kit (GenID GmbH, Germany).

Samples were assessed to determine low- and high-risk HPV types. The results of evaluation were reported as high-risk HPV, including HPV 16, 18, 26, 31, 33, 35, 39, 45, 51–53, 56, 58, 66–70, 73, 82, 85, and 97, and low-risk HPV, including HPV 6, 11, 40, 42, 44, and 54. Some HPV types such as HPV 6, 11, 16, 18, 40, and 45 were recognized specifically and reported separately, but other HPV types were reported as a spectrum of high- or low-risk HPV.

Statistical analysis

First, a one-sample Kolmogorov–Smirnov test (KS) was run to evaluate the normality of quantitative data. Then, based on the results of the KS test, Leven's test and an independent t-test or Mann–Whitney test were applied for normal and abnormal variables, respectively. To compare normal quantitative variables in two groups, we used Leven's test for equality of variances and an independent sample t-test to compare means. To compare abnormal quantitative variables in two groups, we used the Mann–Whitney test. For qualitative variables, we used a chi-squared test. In situations in which a chi-squared test was not possible for 2 × 2 tables, Fisher's exact test was used. Finally, the odds ratios (OR) were computed by logistic regression with a 95% confidence interval (CI). The significance level was considered to be ≤ 0.05 for test analysis. Analysis of data was carried out using SPSS (version 16) software.

Results

The mean age of patients was 25.41 ± 5.48 years in the AGW group with involvement of the UM and 32.45 ± 6.58 years in the AGW group without involvement of the UM (Table 1). All of the patients in both groups had been circumcised due to religious beliefs.

The mean values of duration of lesions in the AGW groups with and without involvement of the UM were 8.95 ± 3.69 and 13.09 ± 5.06 months, respectively (Table 1). Although there was no statistically significant difference between the two groups in terms of age ($p = 1$), weight ($p = 0.55$), and height ($p = 0.1$), a significant difference was seen in the duration of lesions ($p = 0.04$) (Table 1). A large meatus size was found in 18 (81.8%) and eight (36.4%) of cases in the AGW groups with and without involvement of the UM, respectively ($p = 0.004$, OR = 7.875, 95% CI = 1.964, 31.574) (Table 2). Fourteen (63.6%) cases in the AGW group with involvement of the UM and nine (40.9%) cases in the AGW group without involvement of the UM stated that they had had more than one sexual partner during their lifetimes ($p = 0.135$, OR = 2.52, 95% CI = 0.750, 8.522) (Table 2). Anal sexual contact was reported in eight (36.4%) and four (18.2%) patients in the AGW groups with and without involvement of the UM, respectively ($p = 0.183$, OR = 2.57, 95% CI = 0.641, 10.310) (Table 2).

We assessed concurrent STIs in two groups. In the AGW group with involvement of the UM, one (4.5%), two (9.1%), and one (4.5%) patients had gonorrhea, genital herpes, and molluscum contagiosum, respectively. In the AGW group without involvement of the UM, one (4.5%) patient had gonorrhea and one (4.5%) patient had genital herpes.

Of 22 samples in the AGW group with involvement of the UM, HPV infection was detected in eight (36.4%) cases, and low-risk HPV types were found in 75.0% (six of eight patients) and 69.2% (nine of 13 patients) of patients in AGW groups with and without UM involvement, respectively. The characteristics and details of high- and low-risk HPV types in both groups are presented in Table 3.

Table 1 | Demographic data of patients with AGWs with and without involvement of the UM.

Variables	AGWs with UM involvement	AGWs without UM involvement	<i>p</i> value
Mean age (years)	25.41 ± 5.48	32.45 ± 6.58	1
Mean lesion duration (months)	8.95 ± 3.69	13.09 ± 5.06	0.04
Mean weight (kg)	71.64 ± 9.77	73.23 ± 7.83	0.55
Mean height (cm)	174 ± 7.37	171.18 ± 7.07	0.1

AGWs = anogenital warts, UM = urethral meatus, significance level $p \leq 0.05$

Table 2 | Comparison of risk factors in both groups.

Variable	UM involvement in AGWs, n (%), N = 22		OR (95% CI)	<i>p</i> value
	With	Without		
Anal sexual contact	8 (36.4%)	4 (18.2%)	2.57 (0.641–10.310)	0.183
Multiple sexual partners	14 (63.6%)	9 (40.9%)	2.52 (0.750–8.522)	0.135
Large meatus size	18 (81.8%)	8 (36.4%)	7.875 (1.964–31.574)	0.004
Unprotected sexual contact	15 (68.2%)	8 (36.4%)	2.941 (0.505–17.141)	0.230
Concurrent STIs	4 (18.2%)	2 (9.1%)	2.222 (0.363–13.618)	0.388
Marriage	11 (50.0%)	5 (22.7%)	3.4 (0.926–12.489)	0.065

AGWs = anogenital warts, UM = urethral meatus, OR = odds ratios, CI = confidence interval, STIs = sexually transmitted infections, significance level $p \leq 0.05$

Table 3 | Characteristics of HPV types in both groups.

HPV type	AGW with UM involvement	AGW without UM involvement
HPV genome positive <i>n</i>	8	13
Low-risk HPV <i>n</i> (%)	6 (75.0%)	9 (69.2%)
HPV 6 <i>n</i> (%)	3 (50.0%)	4 (44.4%)
HPV 11 <i>n</i> (%)	2 (33.3%)	2 (22.2%)
Other low-risk HPV types <i>n</i> (%)	1 (16.7%)	3 (33.3%)
High-risk HPV <i>n</i> (%)	2 (25.0%)	4 (30.8%)
HPV 16 <i>n</i> (%)	1 (50.0%)	2 (50.0%)
HPV 18 <i>n</i> (%)	0 (0.0%)	1 (25.0%)
Other high-risk HPV types <i>n</i> (%)	1 (50.0%)	1 (25.0%)

AGWs = anogenital warts, UM = urethral meatus, HPV = human papillomavirus

Discussion

To the best of our knowledge, this is the first study to evaluate the risk factors and HPV types in patients with AGWs in the UM region and those with AGWs in other genital areas. The patients in AGW group with involvement of the UM were younger, had multiple sexual partners, and more anal and unprotected sexual contacts; however, these differences were not significantly different compared to the patients in the AGW group without involvement of the UM.

Vives et al. (6) found most patients with UM warts were in their third decade, although a few senile patients with meatus warts had a previous history of urethral instrumentation. Most studies (4, 5, 10, 11) have reported external AGWs to frequently occur in the third and early fourth decades, which is compatible with the results of our study.

In contrast, there was a significant difference in the duration of lesions between both groups. Shorter duration of lesions and earlier attendance of patients affected with AGWs with UM involvement may be related to tumoral mass sensation in the urethra, dysuria, urethral discharge (12), change in the urine stream (13), and concern for malignancy. In addition, larger meatus size was more commonly observed in the AGW group with involvement of the UM than in the AGW group without involvement of the UM. We tend to think a larger meatus size is associated with more direct contact area during intercourse, thereby increasing the risk of infection.

The most important risk factor for AGWs is the number of lifetime multiple sexual partners (10, 14–19). We found that most patients in the AGW group with involvement of the UM and fewer than half of patients in the AGW group without involvement of the UM had multiple sexual partners; however, there were no statistically significant differences between both groups. Our patients in the AGW group with involvement of the UM also more often reported anal sexual contact than those in the AGW group without involvement of the UM, although this observation did not reach statistical significance. Nevertheless, males with external AGWs and a history of anal sexual contact must be evaluated for meatus warts.

In most studies, unprotected sexual contact has been reported as an important factor in AGWs (10, 13, 18, 19). In our study unprotected sexual contact was also a significant factor in the acquisition of genital HPV, especially in the meatus site. We believe protected sexual contact should be an important manner of decreasing meatus AGW involvement.

The incidence of concomitant STIs was comparable between the AGW groups with and without involvement of the UM. Occasionally, genital herpes simplex and molluscum contagiosum were seen with AGWs as coinfection (11, 16, 20).

In our study, there was no difference in the detection of HPV

types between the group of patients with AGWs that involved the UM and those that had AGWs at other locations. Low-risk HPV types were the most commonly detected HPV types (75.0% and 69.2% in the AGW groups with and without UM involvement, respectively). Although low-risk HPV types HPV6 and HPV11 were found to be the causative agents in approximately 90% of AGWs (21), in a study from Latin America, low-risk HPV6 was found in only 56% of men with AGWs (22), which is nearly consistent with our findings. These differences may be related to variations in sex, sexual behavior, taking samples from different areas, and the sensitivity and specificity of the HPV genotyping methods. In addition, based on Aguilar et al.'s (8) findings, the isolation of HPV DNA is less frequent in the meatus area than in external AGWs. We think that the low percentage of low-risk HPV types detection may be related to limited detection of our assay to 28 types of HPV. It is also possible that in our area some low-risk HPV types may be more prevalent, which might not be detected by the assay used.

In our study, high-risk HPV types were detected in a significant proportion of patients with AGWs with and without UM involvement. Our results are similar to the observation by Yaghoobi et al. (23), in which HPV16 was the most frequent surface contamination among patients with AGWs. The prevalence of detected high-risk HPV types as surface contamination was also nearly equal in the meatus and external genital areas.

A small sample size, the recruitment of only circumcised males, and a single-center performance were the limitations of our study.

Conclusion

To conclude, we found that a larger UM size was an important risk factor for the development of AGWs in the UM region; nevertheless, being married, delaying sexual debut, and avoidance multiple sexual partners seemed to be associated with a decreased risk of development of AGWs especially within the UM region. We recommend that further studies be conducted to assess other risk factors and to educate adolescents and young adults regarding STIs and avoidance of high-risk sexual contact. Due to the increasing incidence of AGWs in recent years and difficulty in their eradication, especially in the UM site, an appropriate prevention program should be considered.

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