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Atopic patients with genital warts have a more protracted clinical course and a greater probability of recurrences

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Summary: The factors predicting an unfavourable response of genital warts to treatment have not been determined. The disease characteristics were recorded for 390 patients with genital warts and treated by cryotherapy. The time to achieve clearance was recorded. A personal and family history of asthma, hay fever or eczema, as well as a personal history of common warts and number of recurrences was obtained by telephone four to five years after the clinical visits. In multiple regression analysis, the number of lesions ($P < 0.001$), extent of the disease ($P = 0.003$) and personal history of atopy ($P = 0.001$) were found to influence the time until response to treatment. Similar results were obtained for family history of atopy. The number of sexual partners ($P = 0.007$), extent of the disease ($P = 0.009$) and personal history of atopy ($P < 0.001$) were the main factors influencing the probability of recurrence in multiple logistic regression. The results for family history of atopy were again similar. The study concludes that atopy is a major factor influencing the time frame of the therapeutic response and the probability of recurrence in patients with genital warts.

Keywords: HPV, atopy, genital warts, eczema, asthma

INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted disease. According to mathematical epidemiological models, 80–100% of the sexually active population will be infected by the age of 50.¹ It has been estimated that 2% of the population is infected by HPV types 6 and 11, which are responsible for >90% of genital warts, and that the prevalence of genital warts is 1%.^{2,3} It is obvious that only a small percentage of individuals infected by HPV 6 and 11 ultimately develop clinical disease. The factors that predispose some individuals to clinical disease are largely unknown, but certainly immunity has been implicated. On the other hand, clinicians have realized that all available treatments for genital warts (cryotherapy, podophyllotoxin, electrosurgery, imiquimod and laser) have certain limitations and that 20–30% of the patients relapse and display a more protracted clinical course irrespective of treatment.⁴ There are currently no widely accepted criteria to predict which patients will respond favourably to treatment, when this response will occur and which patients will relapse.

It is a widely held notion among dermatologists that cutaneous viral infections such as viral warts are increased in atopic eczema. However, a debate exists about the susceptibility of atopic individuals to HPV disease, including cervical cancer and common warts, with studies displaying

contradictory results.^{5–7} Prompted by the above data we conducted a clinical study to determine whether atopic individuals (suffering from atopic eczema, asthma or hay fever) with genital warts are more resistant to treatment.

MATERIAL AND METHODS

This retrospective study was conducted at the Sexually Transmitted Disease Unit of Andreas Sygros University Hospital for Skin and Sexually Transmitted Diseases. The study protocol was approved by the Ethical Committee of the Institutional Review Board of Andreas Sygros University Skin Hospital. For all patients attending the unit for genital warts between 2004 and 2006, and who were treated with cryotherapy, information was recorded on age, gender, nationality, number of sexual partners during the past six months, number of genital warts, extent of the disease in cm², location of genital warts (grouped for statistical analysis as follows: for men, 1 = mons pubis, scrotum, genital crurae, 2 = shaft of the penis, prepuce, frenulum, foreskin, 3 = anus, 4 = glans penis, urethra, coronal sulcus; and for women, 1 = mons pubis, genital crurae, labia majora, 2 = labia minora, clitoris, 3 = perineum, 4 = anus; multiple categories were possible) and duration of the disease (months) at the initial visit. Cryotherapy was employed every three weeks until the resolution of the lesions. The time (in months) required to achieve clearance of genital warts was obtained from the medical files. Data on recurrences during the period 2006 to 2009 were collected from the medical files and by contacting the patients by telephone. Patients were also asked by telephone to

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respond to a standard questionnaire about any personal or family history of asthma, eczema or hay fever, after a detailed explanation of the three diseases. Patients were also asked about any personal history of common warts.

STATISTICAL ANALYSIS

The time until clearance of warts and the number of recurrences were examined in relation to: age, gender, the number of sexual partners, the number of warts and their area and location, the duration of the disease, personal and family history of atopy, and personal history of common warts. The association between the time until clearance of genital warts and each factor individually was examined by carrying out simple linear regression with the dependent variable the logarithm of the time until clearance. The logarithmic transformation was used to achieve better conformation to the assumptions of the linear regression model (in particular, normal distribution of the residuals). Multiple linear regression was used to examine the association between the log time until clearance of genital warts and all other factors simultaneously. Because of the limited number of recurrences, the univariate and multivariate associations of recurrences with other factors were examined in logistic regressions with the dependent variable any recurrence versus none. Backward elimination was used to find the most significant predictors in the multivariate regression analyses. Identical results were obtained by forward selection. To examine the effect of atopy, separate analyses were run for each response variable, using personal history or family history. Analyses were run for any history of atopy (hay fever or asthma or eczema) and also for each disease separately. In order to examine the possible association between response and anatomical location of the warts, further analyses were run for men and women separately.

RESULTS

A total of 2500 patients with genital warts attended our department during the study period; 1587 of them were treated solely with cryotherapy. Although we tried to contact all 1587 patients by telephone, only 390 patients were available and were included in the analysis: 315 men aged 18–76 years (mean 32, standard deviation 9.7) and 75 women aged 18–65 (mean 27, standard deviation 8.5). A total of 377 patients were Greek and 11 were immigrants. The median number of sexual partners was 1 (range 0–50), with 19 (4.9%) reporting no partners. The median number of lesions was 5 (1–50), the median extent of the disease was 1.0 cm² (range 0.1–9.0), the median duration of the disease was four months (range 0.25–120) and the median duration of treatment was four months (range 0.5–36). Recurrences were reported by 242 (62.1%) of the patients. Further data on these variables are presented in Table 1. The distribution of the anatomical location of warts is presented in Table 2.

Personal history of atopy was reported by 209 patients (53.6%): hay fever 116 (29.7%), eczema 95 (24.3%) and asthma 50 (12.8%). Family history of atopy was reported by 153 patients (39.2%): hay fever 32 (8.2%), eczema 37 (9.4%) and asthma 110 (28.2%). There was considerable overlap between personal and family history. Family history of atopy was reported by 57.9% of those with a personal history compared with 17.7% of those without. Personal history was reported

Table 1 Demographic, clinical and treatment characteristics of 390 patients with genital warts

	Frequency in total sample		Median duration of treatment (months)	Patients with recurrence n (%)
	n	%		
Total sample	390	100	4	242 (62.1)
Gender				
Male	315	80.8	4	204 (64.8)
Female	75	19.2	4	38 (50.7)
Number of sexual partners				
0	19	4.9	6	11 (57.9)
1	209	53.9	4	117 (56.0)
2	71	18.3	3	43 (60.6)
3+	89	22.9	4	71 (79.8)
Number of lesions				
1	54	13.9	2	17 (31.5)
2–4	119	30.7	3	62 (52.1)
5–9	97	25.0	4	66 (68.0)
10–19	72	18.6	5	53 (73.6)
20+	46	11.9	6	44 (95.7)
Total wart area (cm²)				
0.1–0.4	68	18.8	2	26 (38.2)
0.5–0.9	88	24.4	4	47 (53.4)
1–1.9	95	26.3	5	66 (69.5)
2+	93	25.8	6	84 (90.3)
History of common warts				
No			3	80 (46.2)
Yes			4	162 (74.7)
Disease duration before presentation (months)				
1	94	24.1	3	36 (38.3)
2	43	11.0	4	27 (62.8)
3–4	68	17.4	4	47 (69.1)
5–9	95	24.4	4	71 (74.7)
10–19	56	14.4	5.5	38 (67.9)
20+	34	8.7	5	23 (67.6)
Duration of treatment (months)				
≤1	27	6.9		8 (29.6)
2	72	18.5		34 (47.2)
3	77	19.7		33 (42.9)
4	56	14.4		36 (64.3)
5	40	10.3		30 (75.0)
6+	118	30.3		101 (85.6)
Number of recurrences				
0	148	37.9	3	
1	138	35.4	5	
2	62	15.9	5	
3+	42	10.8	4	

by 79.1% of those with a family history of atopy compared with 37.1% of those without.

Data on the association of atopy with the duration of treatment are presented in Table 3. The univariate associations of atopy and other factors with the logarithm of time until clearance are shown in Tables 1 and 3 (raw data) and Table 4 (regression analyses). The disease extent, the number of lesions, history of common warts, duration of disease, any personal history of atopy and any family history of atopy were all found to be significant factors ($P < 0.001$) predicting the time until response to treatment. Personal history of asthma ($P < 0.001$), eczema ($P < 0.023$) and hay fever ($P < 0.001$), family history of asthma ($P < 0.001$), eczema ($P < 0.029$) and hay fever ($P < 0.003$) were also individually statistically significantly associated with the time until response to treatment (not shown). Among men, location of genital warts on the mons pubis, scrotum and genital crurae was associated with longer duration of treatment ($P = 0.004$), as also was location

Table 2 Anatomical location of genital warts

	Frequency in total sample		Median duration of treatment (months)	Patients with recurrence
	<i>n</i>	%		<i>n</i> (%)
Gender/location				
Men (<i>n</i> = 315)				
Mons pubis, scrotum, genital crurae	70	22.2	5	53 (75.7)
Shaft of the penis, prepuce, frenulum, foreskin	126	40.0	4	88 (69.8)
Anus	42	13.3	5	34 (81.0)
Glans penis, urethra, coronal sulcus	164	52.1	4	99 (60.4)
Women (<i>n</i> = 75)				
Labia majora, mons pubis, genital crurae	37	49.3	3	19 (51.4)
Labia minora, clitoris	32	42.7	4	18 (56.2)
Perineum	23	30.7	4	14 (60.9)
Anus	15	20.0	5	11 (73.3)

Percentages in distribution of locations total more than 100 because multiple locations were possible

on the anus ($P = 0.017$). No location was statistically significantly associated with treatment duration among women. Age ($P = 0.53$), gender ($P = 0.77$) and number of sexual partners ($P = 0.22$) were not found to be significant in univariate analyses. Table 4 shows the antilogarithms (e^b) of the estimated regression coefficients (b); these indicate the multiplicative effect of each factor on the time to clearance of warts. A personal history of atopy increased the expected time until clearance by 44% (i.e. by a factor of 1.44) with 95% confidence interval from 27% to 63% in the univariate analysis.

Considering all factors simultaneously in multiple linear regression, the number of lesions ($P < 0.001$), extent of the disease ($P = 0.003$) and personal history of atopy ($P = 0.001$) were found to influence the time until response to treatment (Table 4). The regression model explained $R^2 = 26.9\%$ of the total variance. Similar results were obtained using family history of atopy ($R^2 = 27.7\%$) and any history (personal or family; $R^2 = 29.4\%$). Once either personal or family history of atopy had been included in the regression model, the other did not statistically significantly improve prediction. In further regression analyses (not shown), the presence of hay fever, asthma and eczema were all statistically significant as separate predictors and the R^2 values were close to those reported above (28.4% for personal history and 27.3% for family history). A personal history of atopy increased the

Table 3 Association of duration of treatment and recurrences of genital warts with personal or family history of atopy

	Duration of treatment (months)		Recurrences
	<i>n</i>	Median (range)	<i>n</i> (%)
Personal history			
–	181	3 (0.5–14)	73 (40.3%)
+	209	4 (1–36)	169 (80.9%)
Family history			
–	237	3 (1–36)	112 (47.3%)
+	153	5 (0.5–24)	130 (85.0%)
Personal or family history			
–	149	3 (1–14)	54 (36.2%)
+	241	5 (0.5–36)	188 (78.0%)

Table 4 Univariate (simple linear regression) and multivariate (multiple linear regression) analyses of factors influencing the therapeutic time frame

	Univariate analyses		Multivariate analysis	
	Relative increase* with 95% CI	<i>P</i>	Relative increase* with 95% CI	<i>P</i>
Age (per additional year)	1.00 (0.99–1.004)	0.53		
Male gender	0.98 (0.83–1.15)	0.77		
Number of sexual partners (per additional partner)	1.01 (0.99–1.03)	0.22		
Number of lesions (per additional lesion)	1.035 (1.03–1.04)	<0.001	1.02 (1.01–1.03)	<0.001
Total wart area (per additional cm ²)	1.25 (1.19–1.32)	<0.001	1.11 (1.03–1.18)	0.003
Duration of disease (per additional month)	1.013 (1.01–1.02)	<0.001		
History of common warts	1.31 (1.15–1.49)	<0.001		
Any personal history of atopy	1.44 (1.27–1.63)	<0.001	1.23 (1.09–1.38)	0.001
Any family history of atopy	1.54 (1.36–1.75)	<0.001		

CI = confidence interval

The dependent variable was the logarithm of the time until clearance of warts. Multiple regression results are shown for statistically significant factors ($P < 0.05$) remaining after backward elimination

*Antilogarithm of estimated regression coefficient

expected time until clearance by 23% (i.e. by a factor of 1.23) with 95% confidence interval from 9% to 38%, adjusting for the other factors in the multivariate analysis. Each extra cm² of wart area increased the expected time to clearance by 11% (3–18%) and each extra wart increased it by 2% (1–3%).

In univariate analyses of recurrences (data in Tables 1 and 3, logistic regression analyses in Table 5), gender was found to influence the probability of recurrences, with men being more susceptible than women ($P = 0.025$). The number of sexual partners ($P = 0.007$), number of lesions ($P < 0.001$) and extent of the disease ($P < 0.001$), and history of common warts ($P < 0.001$) were identified as other significant factors, as well as personal history ($P < 0.001$) or family history ($P < 0.001$) of atopy. Further data on the association between atopy and recurrences are presented in Table 3. Age ($P = 0.23$) and disease duration ($P = 0.14$) were not found to be statistically significant. Among male patients, location on the mons pubis, scrotum and genital crurae ($P = 0.010$) was associated with increased probability of recurrences. Location was not significant among the relatively small sample of female patients.

Considering all factors simultaneously in logistic regression, the number of sexual partners ($P = 0.007$), extent of the disease (0.009) and personal history of atopy ($P < 0.001$) were the most highly significant factors predicting the probability

Table 5 Univariate and multivariate logistic regression analyses for the probability of recurrence of warts

	Univariate analyses		Multivariate analysis	
	Odds ratio with 95% CI	P	Odds ratio with 95% CI	P
Age (per additional year)	0.995 (0.97–1.02)	0.62		
Male gender	1.79 (1.08–2.98)	0.025	1.95 (1.01–3.77)	0.047
Number of sexual partners (per additional partner)	1.19 (1.05–1.34)	0.007	1.27 (1.07–1.50)	0.007
Number of lesions (per additional lesion)	1.15 (1.10–1.20)	<0.001	1.07 (1.00–1.15)	0.043
Total wart area (per additional cm ²)	3.04 (2.14–4.32)	<0.001	1.97 (1.19–3.26)	0.009
Duration of disease (per additional month)	1.02 (0.99–1.04)	0.14		
History of common warts	3.42 (2.23–5.25)	<0.001		
Any personal history of atopy	6.25 (3.97–9.85)	<0.001	5.49 (3.23–9.33)	<0.001
Any family history of atopy	6.31 (3.78–10.5)	<0.001		

CI = confidence interval

Multivariate results are shown for statistically significant factors ($P < 0.05$) remaining after backward elimination

of recurrence. In addition, the number of warts ($P = 0.043$) and gender ($P = 0.047$) were marginally significant (Table 5). The statistical model correctly predicted whether or not the warts would recur in 78.9% of cases (taking estimated probabilities of >0.5 from the logistic regression model as predicting recurrence). Similar results were obtained using family history of atopy instead of personal history (77.5% correct predictions).

DISCUSSION

In our study we found that a personal history of, or predisposition to, atopic diseases (including asthma, hay fever and atopic eczema) was an independent factor influencing the therapeutic response and the relapse rate of genital warts.

Atopy is a state of altered immunity. In atopic dermatitis very low numbers of plasmacytoid dendritic cells, known to play a key role against viral infections, can be detected within the affected skin.⁸ Moreover, plasmacytoid dendritic cells of patients with atopic dermatitis demonstrate a modified immune function, which might contribute to a local deficiency of type I interferons (IFNs), thereby increasing the susceptibility of atopic dermatitis patients toward viral skin infections.⁹ On the other hand, defects in the epidermal barrier, in conjunction with defects in the pattern recognition receptors and reduced production of antimicrobial peptides in the innate immune system of atopics, all contribute to increased susceptibility to cutaneous infections in patients with atopic dermatitis.¹⁰ The physical barrier is the first element of the innate immune system and in atopics is known to be disrupted. Filaggrin,

essential for epidermal barrier formation and hydration, is mutated in a great proportion of atopic cases¹¹ and filaggrin null mutations are associated with more severe asthma and atopic dermatitis.^{12,13} Antimicrobial peptides represent important elements of the skin's immune defence against bacteria, viruses and fungi.¹⁰ In patients with atopic dermatitis antimicrobial peptides, such as defensins, cathelicidins and dermcidin, have all been shown to have diminished expression and function.^{10,14,15} In particular, alpha and beta defensins demonstrate protective activity against papilloma virus.¹⁶ On the other hand in atopic dermatitis a TH2 cytokine pattern predominates with over-expression of interleukin (IL)-4, IL-10 and IL-13,^{17,18} and IL-4 and IL-13 inhibit the tumour necrosis factor (TNF)- α and IFN- γ stimulation in keratinocytes, whereas IL-10 acts indirectly on proinflammatory cytokine production by infiltrating cells.^{17,19} Moreover, high levels of IL-4 and IL-13 inhibit gene expression of inducible nitric oxide synthase which is an important mediator of innate immunity as it can kill viruses through the production of nitric oxide.¹⁰

Disease induced by HPV infection and particular cervical intraepithelial neoplasia (CIN) may be the result of an inappropriate immune response. Indeed, in CIN lesions there is a relative down-regulation of TNF- α , and up-regulation of the TH2 cytokine IL-10, compared with normal cervix,²⁰ and in cervical cancer TH2 infiltrating lymphocytes predominate.²¹

HPV colonization occurs very early in humans and if degenerate consensus polymerase chain reaction sets were available to amplify all of the HPV types found in the skin, this virus would be found almost universally to be a normal inhabitant of all epithelial tissues.²² During the evaluation of HPV in a particular population, two or more distinct HPV types are detected in 95% of lesions.²³ Cell-mediated and humoral immunity may be affected by the types of normal HPV virus that live endogenously within all hosts. Previous investigators have explored the association of atopic diseases with HPV disease. Montgomery *et al.*⁵ found a significant association of a past history of common warts and eczema with cervical cancer. However, hay fever was not identified as a confounding factor and the authors speculated that eczema may not have been atopic. On the other hand, Ivansson *et al.*⁶ found that women with sons suffering from atopy (hay fever, asthma or eczema) were at reduced risk for developing CIN and cancer. They speculated that, because of chronic inflammation, atopic individuals have an increased immunological surveillance for viruses and cancerous cells. In contrast, our study is the first to demonstrate that atopy is an important factor perpetuating HPV disease. A limitation of our study could be that our patients, although demonstrating the clinical features of atopy, have not been proven to bear the primary immunological abnormality of atopy, namely the production of allergen-specific immunoglobulin E, and instead of atopic could be characterized as atopiform.²⁴ Another limitation in our study was that no information was obtained on systemic steroid, topical steroid or inhaled steroid use, which might be an important mediator of treatment response.

We also found that patients with an increased number of genital warts and greater total wart area are more resistant to treatment, consistent with the results of our previous study.²⁵ More restricted total wart area probably represents a reduced viral load and predicts a favourable response. However, the data from the literature are contradictory; because whereas some investigators have found an association between the clearance of genital warts and the size and number of lesions,^{26,27} others have not.²⁸

The location of lesions on the genitalia did not strongly influence the therapeutic response and recurrences. A possible explanation for this finding is that all patients included in the study were treated with cryotherapy, which works equally well on keratinized and non-keratinized areas of the genitalia. Why the number of sexual partners was an important factor in influencing recurrences can be explained by the increased exposure to the virus with an increased number of partners. An increased HPV viral load has been correlated with recurrence previously and oncogenic types have been implicated in recurrent genital warts.²⁹ Moreover, studies have shown that consistent condom use leads to a shorter median time to regression of penile HPV lesions in male contacts of women with CIN, possibly by preventing re-exposure to the virus.³⁰

A further limitation of our study is that it included only 390 individuals out of the target population of 1587. Apart from some refusals to give information, the main reason was that telephone numbers had changed or our calls were not answered. Response would probably have been much better had mobile telephone numbers been available. A low response rate always leaves open the possibility of bias in the findings of a study. However, it seems more likely that any bias would distort the prevalence of recurrences, rather than affecting the associations between recurrences and other factors.

According to the results of our study, when a patient presents with genital warts we may obtain his or her personal or family history of atopy and, if positive, we may warn the patient that their treatment course will be 23% longer than the average time. On the other hand, for atopic cases we may favour treatments on a therapeutic or preventive basis that reduce the number of recurrences, such as imiquimod.

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