Transmission and treatment of cutaneous warts in general practice

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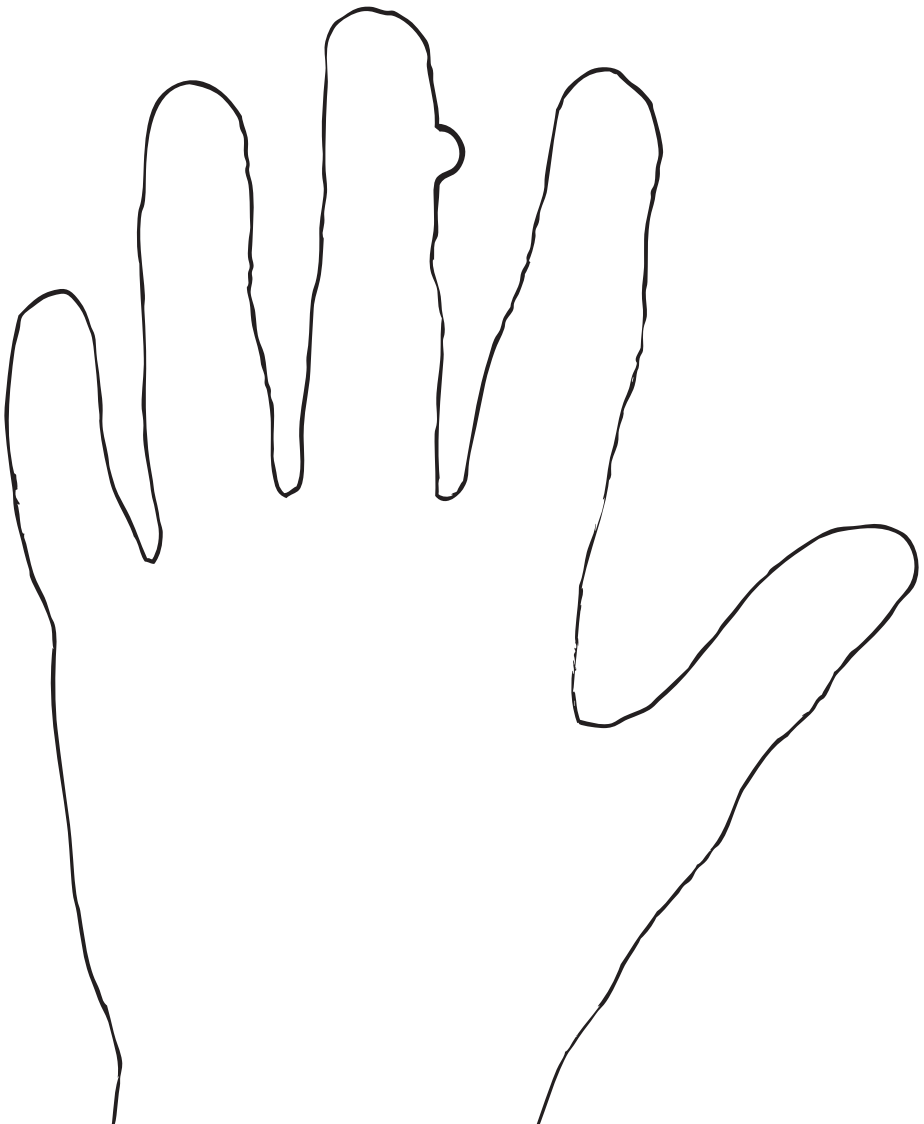

PART TWO

Treatment

CHAPTER 5

Natural course of cutaneous warts among primary schoolchildren: a prospective cohort

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ABSTRACT

Purpose

Because cutaneous warts resolve spontaneously and available treatments often fail, general practitioners and patients may consider a wait-and-see policy. We examined the natural course of cutaneous warts and treatment decisions in a prospective observational cohort of primary school children.

Methods

The hands and feet of children aged 4-12 years from three Dutch primary schools were inspected for the presence of warts at baseline and after a mean follow-up of 15 months. Parental questionnaires at follow-up provided information on inconvenience caused by warts and treatments used.

Results

Of the 1134 eligible children, 1099 participated (97%) of which 366 (33%) had cutaneous warts at baseline. Overall, loss to follow-up was 9% and response from parental questionnaires was 83%. The complete resolution rate was 52 per 100 person-years at risk (95% CI 44-60). Age (hazard ratio 1.1 per year decrease, 95% CI 1.0-1.2) and non-Caucasian skin type (hazard ratio 2.0, 95%CI 1.3-2.9) were related to higher resolution rates. During follow-up, 38% of children with warts at baseline decided to treat warts: 18% used over-the-counter treatment, 15% treatment in general practice, and 5% used both. Initiation of treatment was related to warts ≥1cm in size and parent-reported inconvenience caused by warts.

Conclusions

Half of primary school children with warts will be free of warts within one year. Young age and non-Caucasian skin type enhance resolution. Children with large or inconvenient warts are more likely to start treatment. These findings will be useful in the process of shared decision-making with parents and children.

INTRODUCTION

Cutaneous warts are caused by the human papillomavirus (HPV). Small defects of the skin are sufficient for HPV to infect the basal layer of the skin which may lead to benign hyperkeratotic papillomas.[1] Warts are very common in the general population, especially among children. The prevalence of warts among primary school children is reported to be 22-33%,[2;3] while the annual prevalence based on consultations in general practice is about 6%.[4;5] This difference indicates that only a proportion of children seeks medical advice or treatment for warts.

Liquid nitrogen cryotherapy and salicylic acid application (30-50%) are the most frequently used treatments for warts by general practitioners (GPs).[6] Less potent over-the-counter (OTC) cryotherapy or salicylic acid (usually 17%) treatments are offered in pharmacies without prescription.[7] Because warts resolve spontaneously and available treatments often fail, especially in the case of plantar warts,[8-10] a 'wait-and-see' policy may be considered in treatment decisions.[11] However, studies on the natural course of warts are scarce and outdated.[12-14]

Therefore, the present study examines the natural course of cutaneous warts and treatment decisions in a prospective observational cohort of primary school children.

METHODS

Study cohort and procedures

At baseline we included all children in grades 1-7 from three primary schools in/around the city of Leiden, the Netherlands. A trained medical student inspected the hands and feet of all children for the presence of warts. A previous publication reports on the details of the baseline examination.[3] One year later, another trained medical student examined the hands and feet of all children with warts at baseline (now in grades 2-8), again for the presence of warts. Mean follow-up was 15 months, with a range of 11-18 months due to practical reasons and taking into account school vacations. Parents were asked to give informed consent before both examinations. Apart from this, children were free to refuse participation during examinations. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center, as well as by the boards of the participating schools.

Presence of warts

At baseline and follow-up, the type and number of warts were recorded on standard forms with schematic representation of the hands and feet. A distinction was made between plantar warts (located on the sole of the feet) and common warts (located on the hands

or the dorsal side of the feet). Complete resolution was defined as a child with no warts at follow-up examination. A wart was considered resolved when it was no longer visible (skin favour and skin lines were re-established) and could no longer be palpated by hand. Over 5% of both the baseline and the follow-up examinations were supervised by experienced GPs, with no discordance regarding wart diagnosis or resolution.

Factors enhancing resolution

During baseline examination, the following factors were recorded:

- Demographic factors: age (split on the median: 4-7 years vs. 8-12 years), sex (girls vs. boys), and skin type (coded according to Fitzpatrick to stratify into Caucasian vs. non-Caucasian subgroups).[15]
- Wart factors: type (plantar vs. common warts), number of warts (single vs. multiple warts), size of wart (<1 cm vs. ≥1 cm).

Treatment decisions

Prior to follow-up examination, parents were asked to complete a questionnaire about the inconvenience caused by warts present at any time during the follow-up period and which treatments were initiated for these warts. The following factors were recorded:

- Inconvenience of warts: type of inconvenience (pain, irritation, unsightly, opinion of others), and amount of inconvenience (on a scale from 0 [no inconvenience] to 4 [considerable inconvenience]);
- Initiated treatment: GP involved (OTC treatment vs. GP treatment), specific treatment (cryotherapy vs. salicylic acid application vs. others),

Statistical analyses

Resolution rates with 95% confidence interval (CI) were calculated, dividing the children with complete resolution by the sum of the person-time of children at risk (person-years at risk). For calculating person-time at risk, the date of resolution was considered to be halfway the follow-up period. In addition, we calculated resolution rates stratified for plantar and common warts, as well as the resolution rate when only baseline warts were considered, i.e. new warts which developed during the follow-up period were disregarded. Cox proportional hazards models were used to identify factors enhancing resolution. Univariate analysis was performed for demographic, wart, and treatment factors to estimate hazards ratios (HR) with 95% CI. Multivariate analysis with all factors was performed to assess which relations were independent. In subgroup analysis, HRs were calculated for children with plantar warts separately. In addition, a logistic regression model was used to

explore factors related to the decision to treat warts. Odds ratios (OR) with 95% CI were calculated for demographic, wart, and inconvenience factors.

RESULTS

Study cohort

At baseline, the participation rate of 1134 eligible children was 97%: 23 children (2%) were absent from school at the time of baseline examinations, and for 12 children (1%) parental or child consent was not given. At baseline, 366 children had warts upon examination (33%). During follow-up, 33/366 (9%) were lost to follow-up: 24 children (7%) left school and for 9 children (2%) parental or child consent was not given for the follow-up

Table 5.1. Baseline characteristics of the primary school children with warts included in the follow-up (n=333)

Median age in years (range)	8 (4-12)
Sex	
Boys	162 (49)
Girls	171 (51)
Skin type	
Caucasian	284 (85)
Non-Caucasian	49 (15)
School	
School A, 28 classes	219 (66)
School C, 8 classes	27 (8)
School D, 12 classes	87 (26)
Type of warts	
Common warts	100 (30)
Plantar warts	192 (58)
Both common and plantar	41 (12)
Number of warts	
1 wart	191 (57)
2 warts	63 (19)
3 to 5 warts	52 (16)
6 warts or more	27 (8)
Size of warts	
No warts ≥1 cm	209 (63)
Wart ≥1 cm	124 (37)

Values are numbers (%), unless stated otherwise

examination. At baseline, the median age of the 333 children included in the follow-up was 8 years (interquartile range [IQR] 5-10 years), 49% was male, and 15% had a non-Caucasian skin type, originating from Morocco, Turkey, China, the Netherlands Antilles or Surinam (Table 5.1). In total, 42% of the children had common warts, 70% plantar warts, 43% multiple warts, and 37% had a wart ≥1 cm in size.

Resolution of warts

The complete resolution rate was 52 per 100 person-years, 95% CI 44-60. When newly-developed warts were not considered, the resolution rate of baseline warts was even higher: i.e. 90 per 100 person-years (95% CI 79-100). These numbers were similar for both common warts and plantar warts.

Table 5.2. Univariate analysis of the association of demographic and wart factors at baseline with the resolution of all warts in primary school children

Potential risk factor	No. of cases/ Person-years	Resolution rate per 100 person-years	Hazard ratio* (95% CI)	p-value
Demographic factors				
Age in years				
8-12	80 / 176	45	1	
4-7	82 / 137	60	1.5 (1.1-2.0)	0.015
Per year decrease			1.12 (1.04-1.20)	0.003
Sex				
Girls	76 / 164	46	1	
Boys	86 / 149	58	1.3 (0.9-1.7)	0.13
Skin type				
Caucasian	129 / 274	47	1	
Non-Caucasian	33 / 39	85	2.0 (1.3-2.9)	0.001
Wart factors				
Type				
Common	50 / 94	53	1	
Plantar	96 / 181	53	1.0 (0.7-1.4)	0.88
Both common and plantar	16 / 38	42	0.7 (0.4-1.2)	0.19
Number				
Single wart	90 / 184	49	1	
Multiple warts	72 / 129	56	1.1 (0.8-1.4)	0.71
Per extra wart †			1.03 (0.96-1.10)	0.43
Size				
≥1 cm	55 / 117	47	1	
<1 cm	106 / 194	55	1.2 (0.9-1.6)	0.29

* Generated by univariate Cox proportional hazards model.

Factors enhancing resolution

Young age (HR 1.1 per year decrease, 95% CI 1.0-1.2) and non-Caucasian skin type (HR 2.0, 95% CI 1.3-2.9) enhanced the resolution of warts, whereas the type, number or size of the warts did not predict resolution (Table 5.2). Multivariate analysis showed almost comparable results with the only difference being that, in this model, an increase in the number of warts slightly enhanced the resolution (HR 1.1 per extra wart, 95% CI 1.0-1.2, p=0.039). Subgroup analysis of children with plantar warts and the analysis only considering warts present at baseline yielded similar results as primary analysis considering all warts including warts that developed during follow-up.

Treatment decisions

According to parental questionnaires with a response of 276/333 (83%), 73 children (26%) reported inconvenience caused by warts and 106 (38%) children were treated with OTC or GP treatments during follow-up (Table 5.3). Two children were referred to

Table 5.3. Reported inconvenience caused by warts and initiated treatments according to parental questionnaires* (n=276)

Any inconvenience caused by warts	73 (26)
Pain	23 (8)
Irritation	28 (10)
Unsightly	38 (14)
Bothered by opinion of others	10 (4)
Initiated treatment	106 (38)
OTC treatment only	49 (18)
GP treatment only	41 (15)
GP as well as OTC treatment	16 (5)
Specific OTC treatments‡	
Dimethylether/propane cryotherapy	28 (10)
Low dose (17%) salicylic acid	37 (13)
Duct tape	2 (1)
Other	12 (4)
GP treatments‡	
Liquid nitrogen cryotherapy	49 (18)
High dose (40-50%) salicylic acid	14 (5)
Other	3 (1)

* Response to parental questionnaires was 276/333 (83%)
† Initiated treatments were comparable for common warts and plantar warts
‡ More than one option possible: 23 children reported more than one type of inconvenience, 13 children used more than one OTC treatment, and 9 children used more than one GP treatment.

Table 5.4. Associations of personal and wart factors at baseline and reported inconvenience with the decision to treat warts during follow up (n=276)

	Odds ratio* (95% CI)	p-value
Demographic factors		
Age (per year increase in age)	1.1 (0.9-1.2)	0.33
Female sex	1.3 (0.8-2.1)	0.28
Caucasian skin type	1.6 (0.8-3.2)	0.24
Wart factors		
Plantar location	1.1 (0.7-2.0)	0.66
Number (per extra wart)	1.1 (1.0-1.2)	0.080
Size ≥1 cm	3.2 (1.9-5.3)	<0.001
Warts not resolved at follow-up†	2.0 (1.2-3.3)	0.012
Inconvenience caused by warts§		
Yes	38 (16-90)	<0.001
Degree of inconvenience‡	11 (5.6-23)	<0.001
Pain	21 (4.8-91)	<0.001
Irritation	27 (6.3-118)	<0.001
Unsightly	20 (6.7-57)	<0.001
Opinion of others	16 (2.0-126)	0.010

* Generated by univariate logistic regression model.
† Proxy for long-lasting warts
‡ OR per unit on a scale from 1 (little inconvenience) to 4 (considerable inconvenience).
§ Reported retrospectively by parents

a dermatologist. Initiated treatments were comparable for common warts and plantar warts. Children treated during the follow-up period had worse resolution rates than the non-treated children: HR for all treatments 0.6 (95% CI 0.4-0.8); for GP treatments 0.7 (95% CI 0.4-1.1) and for OTC treatment only 0.5 (95% CI 0.3-0.8).

The decision to initiate treatment of warts during follow-up (OTC and GP treatment combined) was not related to age, sex, skin type, or type of wart at baseline, but was related to the size of the wart at baseline (OR ≥1 cm vs. <1 cm 3.2, 95% CI 1.9-5.3), long-lasting warts (OR not resolved vs. resolved warts at follow-up 2.0, 95% CI 1.2-3.3), and the reported inconvenience caused by warts (OR inconvenience vs. no inconvenience 38, 95% CI 16-90, Table 5.4). Multivariate analysis with all of the above factors showed comparable results.

DISCUSSION

Summary of findings

Half of all primary school children with warts will be free of warts after one year. Among young children and children with non-Caucasian skin type, resolution rates are even higher. During follow-up, 38% of children/parents decided to treat warts, a decision that was related to bigger size of warts and increased inconvenience caused by warts.

Comparison with other studies

The most cited study on the natural course of cutaneous warts reported 113/168 (67%) of patients free of warts after 2 years.[12] None of the participants were treated during follow-up; however, that study was conducted in 1963 in an institutionalised mentally disabled population. Another study conducted in 1959 with a complete resolution after one year of 77/136 (57%) only included hand warts in Dutch primary school children,[13] and a more recent cohort of 11-year-old British children showed a 5-year resolution of 337/364 (93%) but did not provide data on a shorter follow-up.[14] Despite all the methodological limitations, the natural course in these latter studies is roughly in line with that in our study. Although the full complexity of the relationship between the persistence of warts and immunologic responses is not yet fully elucidated,[16] the current study shows that age and ethnic factors play a role in the resolution of warts. In agreement with others, the location and size of warts do not seem to influence the resolution rate.[12;13] Associations with the number of warts are not consistent in other studies and the present study could not provide clear evidence on this issue either. [10;12;13]

Strengths and limitations

This study with a participation rate of 97% represents the natural course of warts in a current primary school population in Western Europe. Although the data did not allow to draw conclusions on time to resolution or wart growth, resolution rates after one year were objectively established by physical inspection of hands and feet. Warts on other parts of the body were potentially missed, but they only account for less than 4% of all warts.[17] Information on initiated treatments was collected because treatment effects might play a role in the observed resolution rates. In agreement with a study among Australian school children,[2] about one third of children with warts had sought treatment, for which a wide range of OTC and GP treatments were available. The remaining two thirds decided to refrain from treatment, or were simply not aware of the presence of warts. The parental questionnaires before baseline examination at least showed that approximately half of

all children had warts that had not been noticed earlier by their parents.[3] The present study shows that family practice yearly only encounters 20% of all children with warts. These children have larger and more inconvenient warts with poorer resolution rates than children who did not seek treatment. However, further interpretation of these findings is limited because selection and recall bias are probably involved. We had no information on the duration of warts at baseline; moreover, retrospectively, the parents of children with persistent warts may more easily have recalled treatments and inconvenience than the parents of children with resolved warts. In a recent randomised controlled trial in a GP population the resolution rate in children after a wait-and-see policy of 3 months was 29% (95% confidence interval 17% to 45%).[10]

Implications

A child with warts has a 50 percent chance of still having warts after waiting a year, despite any treatments. Warts in young children and children with Caucasian skin types will resolve faster. These findings will be useful in the process of shared decision-making with parents and children. Patients and GPs should weigh the benign natural course, the side effects of treatments and costs on the one hand, and the effectiveness of treatments and the risk of spreading warts on the other. Future research needs to more precisely establish time to resolution of warts and identify subgroups of patients with relatively low natural resolution rates and high treatment response.

REFERENCES

(1) Androphy EJ, Lowy DR. Warts. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. Fitzpatrick's Dermatology in General Medicine. Seventh ed. USA: McGraw-Hill; 2008: 1914-23.

(2) Kilkenny M, Merlin K, Young R, Marks R. The prevalence of common skin conditions in Australian school students: 1. Common, plane and plantar viral warts. Br J Dermatol 1998;138:840-45.

(3) van Haalen FM, Bruggink SC, Gussekloo J, Assendelft WJ, Eekhof JA. Warts in primary school-children: prevalence and relation with environmental factors. Br J Dermatol 2009;161:148-52.

(4) Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der ZJ. Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. Eur J Public Health 2005;15:59-65.

(5) Schofield J, Grindlay D, Williams HC. Skin conditions in the UK: a health care needs assessment. Nottingham: Centre of Evidence Based Dermatology, University of Nottingham; 2009.

(6) Bruggink SC, Waagmeester SC, Gussekloo J, Assendelft WJ, Eekhof JA. Current choices in the treatment of cutaneous warts: a survey among Dutch GP. Fam Pract 2010;27:549-53.

(7) Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ et al. Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model. Health Technol Assess 2006;10:iii, ix-87.

(8) Gibbs S, Harvey I. Topical treatments for cutaneous warts. Cochrane Database Syst Rev 2006;3: CD001781.

(9) Cockayne S, Curran M, Denby G, Hashmi F, Hewitt C, Hicks K et al. EVerT: cryotherapy versus salicylic acid for the treatment of verrucae - a randomised controlled trial. Health Technol Assess 2011;15:1-170.

(10) Bruggink SC, Gussekloo J, Berger MY, Zaaijer K, Assendelft WJ, de Waal MW et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomised controlled trial CMAJ. 2010;182:1624-30.

(11) Patient information leaflet on plantar warts [internet, updated 2012]. British Association of Dermatologists; Available from: http://www.bad.org.uk/site/859/Default.aspx

(12) Massing AM, Epstein WL. Natural history of warts. A two-year study. Arch Dermatol 1963;87: 306-10.

(13) van der Werf E. Een onderzoek naar het voorkomen en het verloop van wratten bij schoolkinderen [Studies on the incidence and course of warts in school children]. Ned Tijdschr Geneeskd 1959;103:1204-08.

(14) Williams HC, Pottier A, Strachan D. The descriptive epidemiology of warts in British schoolchildren. Br J Dermatol 1993;128:504-11.

(15) Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988;124:869-71.

(16) Burkhart CG. The endogenous, exogenous, and latent infections with human papillomavirus. Int J Dermatol 2004;43:548-49.

(17) Larsson PA, Liden S. Prevalence of skin diseases among adolescents 12-16 years of age. Acta Derm Venereol 1980;60:415-23.