

Incidence of trichiasis in a cohort of women with and without scarring

Beatriz Muñoz,^a Linda Bobo,^b Harran Mkocha,^c Matthew Lynch,^a Yu-Hsiang Hsieh^d and Sheila West^a

Background Blindness from trachoma is a significant problem for many underdeveloped countries. While active trachoma is common in children, trichiasis, the potentially blinding sequella, develops in adulthood and affects mainly women. Little is known about factors associated with the development of trichiasis.

Methods The 7-year incidence of trichiasis and its association with ocular chlamydia infection was examined in a cohort of women from a hyperendemic area. A total of 4932 women 18 years and older, living in 11 villages in Central Tanzania, were examined in 1989. A follow-up examination in 1996 was performed on all women with scars living in six of the 11 villages and on a random sample of women without scars from the same villages. Trachoma was graded clinically, chlamydia infection was ascertained at follow-up using polymerase chain reaction-enzyme immunoassay (PCR-EIA).

Results A total 523 of the women with scars and 503 of the women without scars were re-examined. Forty-eight of the women with scars (incidence, 9.2%) and three of the women without scars (0.6%) developed trichiasis in the 7-year period. Prevalence of chlamydia infection was significantly higher in the group with scars (11.7% versus 7.1%). Trichiasis cases were more likely to be older, and to have chlamydia infection at follow-up odds ratio (95% confidence interval) 2.5 (1.1–5.7).

Conclusion The 7-year incidence rate in the population with scars was high, over 1% per year. Ocular chlamydia infection was more common in the group with scars at baseline and was also associated with being a trichiasis case, suggesting the importance of potentially long-term chlamydia infection in the progression to trichiasis. Antibiotic distribution programmes for trachoma control should include women with scars.

Keywords Trachoma, scars, trichiasis incidence, ocular chlamydia infection

Accepted 29 June 1999

Blindness from trachoma is a significant problem for many countries of Africa and Asia.¹ Caused by repeated infection with *Chlamydia trachomatis*, trachoma is hyperendemic in many of the disadvantaged communities of these countries. Chlamydial infection, and the clinical manifestation of follicular and inflammatory trachoma, are most common in pre-school children.^{2,3} Scarring of the upper eyelid from repeated episodes of infection can be seen in young adults. However, the potentially blinding complications trichiasis and entropion (eye lashes touching the cornea and in-turned eye lids), are seen in middle-aged people, predominantly women.³ When left untreated, trichiasis/

entropion may lead to corneal damage and irreversible vision loss. The long latent period from pre-school to middle-age and older has made the study of risk factors for trichiasis difficult. Thus, very little is known about the incidence of trichiasis in hyperendemic areas, and risk factors associated with the development of these blinding complications. Specifically, it is not known how scarring in young adults leads to later trichiasis, and what role ongoing ocular chlamydia infection plays in this process.

This study represents a unique opportunity to document the incidence of trichiasis and associated risk factors in a cohort of women living in a trachoma hyperendemic region. The cohort was first examined for trachoma in 1989 and then re-examined 7 years later.

Methods

As part of a case-control study to examine social risk factors for trichiasis in women,⁴ a complete house-to-house census of all

^a Dana Center for Preventive Ophthalmology, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21205, USA.

^b Stanley Research Foundation, NAMI Research Institute, 5439 Grosvenor Lane, Suite 200, Bethesda, MD 20814, USA.

^c Dodoma Regional Hospital, Dodoma, Tanzania.

^d Adult Infectious Diseases, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, MD 21205, USA.

women 18 years and older was carried out in 1989 in 11 villages from the Kongwa district of Central Tanzania. All women that were part of the census were asked to participate in an eye examination to screen for the presence of signs of trachoma. Of 6038 women listed in the census, 82% had ocular examinations.

Each eye was examined for the presence of trachoma using the WHO simplified grading scheme.⁵ The following trachoma signs were graded: trichiasis, or presence of at least one eye lash rubbing the eyeball; corneal opacities, or presence of a central opacity sufficiently dense to obscure the pupil margin; follicular trachoma, or the presence of five or more follicles (0.5 mm or greater in diameter) on the central upper tarsal conjunctiva; severe inflammation, or presence of inflammatory thickening of the upper tarsal conjunctiva with obstruction of more than half of the normal tarsal vessels; scarring, or presence of easily visible scars in the upper tarsal conjunctiva. Eye examinations were performed by a trained eye nurse using binocular loupes with 2.5 magnification and a penlight. The examiner has been shown to have good intra-observer reliability and inter-observer reliability when standardized against a senior trachoma grader.⁶ At that time 205 women were identified as having trichiasis and these women were excluded from the current study.

Due to time and budget constraints only a subset of the original cohort was selected for follow-up in 1996. From six of the original 11 villages which were accessible to the study team, all cases of scars (745) plus a random sample of 749 women without scars in the same six villages were selected for follow-up. The project team attempted to re-contact all the selected women in 1996. The women were re-graded clinically for the presence of follicular trachoma, severe inflammation, conjunctival scars and trichiasis, using grading procedures identical to the ones used at baseline. The examiner, an experienced trachoma grader, was masked to the baseline status of the women. In addition, conjunctival swabs were taken for the determination of chlamydial infection using the polymerase chain reaction-enzyme immunoassay (PCR-EIA) for a conserved 280 bp region of the major outer membrane protein-1 gene fragment of *C. trachomatis*.⁷ We have previously shown a strong relationship between the strength of the fluorescent signal from the PCR-EIA and the severity of clinical trachoma.⁷ In this study, we use the signal (in fluorescent units) as a semi-quantitative measure of intensity of infection. Additional data collected at follow-up included: questions on raising cattle, cattle pens near the home, number of children, age of their youngest child, child care responsibilities in the past and currently, family history of trichiasis and education.

Data analysis

The age stratified 7-year incidence of trichiasis is presented for the group of women with scars at baseline. Contingency tables analysis was performed to examine crude associations. Two separate logistic regression models were used to predict presence of trichiasis among the women with scars as a function first, of baseline characteristics, and second, of follow-up characteristics. The association of ocular chlamydia infection at follow-up with presence of active disease and scars at baseline, age, and environmental factors was examined using a logistic model. Results are presented as odds ratios and 95% confidence intervals.

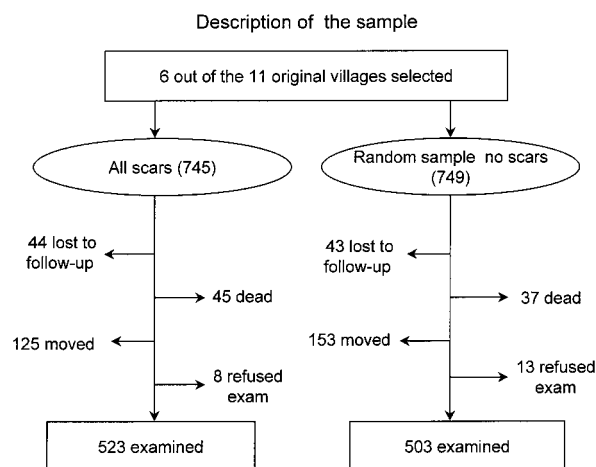


Figure 1 Follow-up experience of the selected sample

Results

The follow-up experience of the selected cohort of 745 women with scars and 749 without scars is shown in Figure 1. Overall 1026 of the 1494 women selected for follow-up were re-examined (69% of the sample). Most of the losses were due to moves from village of residence to unknown whereabouts. The death rates in both groups were similar, and only 1.5% and 2.5%, respectively of the women that we were able to contact refused to be re-examined. There was no differential response by known baseline characteristics (Table 1). There was no significant difference in the age distribution of responders and non-responders. Similar prevalences of active disease at baseline, around 5.0%, were observed in the groups examined and in the group lost to follow-up.

In the group of 1026 women with data at both time points, 9.5% had active chlamydial infection at follow-up. The 7-year incidence of new cases of trichiasis was 9.2% in women who had scars in 1989, compared to three cases, or 0.6% in women without scars. Given the few cases of trichiasis in the women without scars at baseline, the next set of analysis is restricted to

Table 1 Baseline characteristics by follow-up status and presence of scars at baseline

| Baseline characteristic | No scars at baseline | | Scars at baseline | |
|-----------------------------|----------------------|--------------|-------------------|--------------|
| | Examined | Not examined | Examined | Not examined |
| Number selected | 503 | 244 | 523 | 222 |
| Age group (in years) | | | | |
| >20 | 16.8% | 20.1% | 5.9% | 5.9% |
| 20–29 | 37.2% | 41.8% | 23.7% | 17.6% |
| 30–39 | 22.6% | 18.4% | 22.6% | 21.6% |
| 40–49 | 12.5% | 10.3% | 22.2% | 23.9% |
| 50–59 | 7.3% | 7.0% | 15.1% | 18.0% |
| <60 | 3.6% | 2.5% | 10.5% | 13.1% |
| Active trachoma | | | | |
| Absent | 94.7% | 94.7% | 95.4% | 95.0% |
| Active trachoma | 5.3% | 5.3% | 4.6% | 5.0% |

Table 2 Incidence of trichiasis between 1989 and 1996 among women with scars at baseline by baseline and follow-up characteristics

| Characteristics | No. | % incidence | Odds ratio (95% CI) ^a |
|-------------------------------------|-----|-------------|---|
| Age at baseline (in years) | | | |
| <20 | 31 | 6.5 | |
| 20–29 | 124 | 6.5 | |
| 30–39 | 118 | 6.8 | |
| 40–49 | 116 | 10.3 | |
| 50–59 | 79 | 8.9 | |
| 60+ | 55 | 20.0 | Test for trend $\chi^2_{(1)} = 6.4, P = 0.011$ |
| Active trachoma at baseline | | | |
| No | 499 | 8.6 | 1.00 |
| Yes | 24 | 20.8 | 3.21 (1.11–9.24) |
| Active trachoma at follow-up | | | |
| No | 422 | 7.1 | |
| Yes | 101 | 17.8 | 3.03 (1.60–5.80) |
| Follow-up infection status | | | |
| Negative | 453 | 8.4 | 1.00 |
| Positive | 60 | 15.0 | 2.36 (1.05–5.29) |
| Cattle near home | | | |
| No | 394 | 8.4 | 1.00 |
| Yes | 127 | 11.8 | 1.69 (0.87–3.27) |
| Child care responsibilities | | | |
| No | 152 | 14.5 | 1.00 |
| Yes | 368 | 7.1 | 0.56 (0.28–1.14) |
| Family history of trichiasis | | | |
| No | 461 | 8.5 | 1.00 |
| Yes | 60 | 15.0 | 2.06 (0.93–4.54) |
| Overall | 523 | 9.2 | |

^a Age adjusted odds ratios and 95% confidence intervals.

the trichiasis cases in the group with scars at baseline. The age-specific 7-year incidence rate in women with scars at baseline rose from 6.5% in women less than 40 years of age to 20% in women 60 years and older (Table 2). This is an average rate of 1.3% per year among women with scars, in a cohort with the age characteristics of our group. After controlling by age, presence of active disease at baseline was a significant predictor of the 7-year incidence of trichiasis, odds ratio 3.2 (1.1–9.2).

Factors assessed at follow-up which were associated with being an incident case of trichiasis included active disease, positive chlamydia infection, having cattle near the home, and a family history of trichiasis (Table 2). Only active disease, and presence of chlamydia infection at follow-up were significant after age adjustment. Child care responsibilities were no longer protective, after age adjustment. Obviously, active disease and infection are highly correlated. Therefore, for the multivariate model of trichiasis using risk factors assessed at follow-up, only infection status was used. Among women with scars, the strongest association with trichiasis was the presence of chlamydial infection, with an odds of 2.5 (1.1–5.7) (Table 3). Trichiasis was also associated with increasing age. Having cattle near the home and reporting a family history of trichiasis also increased the

Table 3 Multivariate model of factors assessed at follow-up associated with developing trichiasis in the 523 women with scars

| Characteristic | Odds ratio (95% confidence interval) |
|------------------------------|--------------------------------------|
| Age (increase per year) | 1.03 (1.01–1.06) |
| Chlamydia infection | 2.51 (1.10–5.69) |
| Cattle near home | 1.87 (0.96–3.67) |
| Family history of trichiasis | 2.00 (0.87–4.62) |

Table 4 Characteristics associated with prevalence of chlamydia infection by presence of scars at baseline

| Follow-up characteristics | No scars (n = 503) ^a | | Scars (n = 523) ^a | |
|---|---------------------------------|------------|------------------------------|------------|
| | No. | % infected | No. | % infected |
| Age at follow-up (in years) | | | | |
| 20–29 | 162 | 11.2 | 63 | 20.6 |
| 30–39 | 168 | 6.0 | 150 | 15.3 |
| 40–49 | 95 | 5.3 | 107 | 11.2 |
| 50–59 | 43 | 4.7 | 106 | 6.6 |
| 60+ | 33 | 3.0 | 87 | 5.8 |
| Active disease at follow-up | | | | |
| None | 453 | 3.8 | 414 | 5.8 |
| Follicular | 16 | 31.3 | 6 | 33.3 |
| Severe | 32 | 43.8 | 93 | 36.6 |
| Trichiasis at follow-up | | | | |
| Absent | 499 | 7.2 | 466 | 10.9 |
| Present | 2 | 0.0 | 47 | 19.2 |
| Cattle near home | | | | |
| No | 350 | 7.7 | 385 | 12.7 |
| Yes | 149 | 6.0 | 126 | 8.7 |
| Having at least one pre-school child | | | | |
| No | 88 | 2.3 | 148 | 6.1 |
| Yes | 405 | 8.4 | 359 | 14.2 |
| Overall | 501 | 7.2 | 513 | 11.7 |

^a Two women in the no scars group and 10 women in the scars group had missing laboratory specimens.

odds of developing trichiasis, but these associations were not statistically significant. No other factors measured at follow-up were significantly associated with trichiasis in this model.

The high rate of active infection (9.5%) in this group of older women at follow-up was somewhat surprising. Moreover, as it appeared to be an important factor, further studies were carried out to determine the characteristics associated with infection at follow-up, in women with and without scars (Table 4). Infection, in both the group of women with scars at baseline and the women with no scars at baseline declined with age (test for trend $P = 0.001$ and $P = 0.03$, respectively) although the women with scars at baseline were twice as likely in each age group to have active infection.

As noted before, presence of chlamydia infection was associated with active disease. About one-third of women with follicular trachoma had evidence of chlamydia infection, and anywhere from 37% to 44% of those with severe inflammatory trachoma. Follicular trachoma was rare in either group of

Table 5 PCR-EIA signal in women with ocular chlamydia infection by clinical trachoma status

| Clinical trachoma status | No. | Mean (SD) | (Minimum, maximum) |
|--|-----|-------------|--------------------|
| No scars at baseline, no trichiasis at follow-up | 36 | 878 (871) | (25, 3778) |
| Scars at baseline, no trichiasis at follow-up | 51 | 1208 (1292) | (17, 4000) |
| Scars at baseline, trichiasis at follow-up | 9 | 2178 (1397) | (19, 3859) |

women and active disease was characterized by severe trachoma. Unlike in pre-school children, the rate of chlamydial infection in women who had no active disease was low, between 4% and 5%. Infection was not related to having cattle near the home but was strongly associated with the presence of pre-school children at home. The prevalence of chlamydial infection at follow-up in this cohort of women was modelled as a function of age, presence of active disease at baseline, presence of scars at baseline, and presence of pre-school children at follow-up. Decreasing age, presence of active disease at baseline, and presence of scars at baseline were significantly associated with infection at follow-up (data not shown).

The strength of the PCR-EIA signal, in fluorescent units, was compared in those with infection in three groups: those with no scars at baseline and no trichiasis at follow-up; those with scars at baseline and no trichiasis at follow-up; and those with scars at baseline and trichiasis at follow-up (Table 5). The intensity of infection was the least in the infected group with no scars and no trichiasis. There was a significantly higher count among infected women with both scars and trichiasis, suggesting more intense infection.

Discussion

In a 7-year follow-up of a cohort of women living in a trachoma hyperendemic area, the rate of trichiasis over a 7-year period is estimated at 1.3% per year, confined to women with scars. The incidence rate tends to increase with age among women with scars. We did not have grading of the severity of scars at baseline, so some of the increase in trichiasis with age may reflect more severe scarring in the older age group. We were able to locate and examine only 69% of the women in the selected sample. In a population with high migration, locating 69% after 7 years is quite acceptable. The fact that the known characteristics of women lost to follow-up were similar to those of women that we were able to examine, suggests that our incidence figures are reasonable estimates of the incidence of trichiasis in women.

Incident trichiasis cases tended to occur in those reporting a family history of trichiasis, although the odds were not significantly different from one. Recall of a family history of trichiasis is subject to bias if the cases are more likely to recall other family members with the disease because of their affliction. However, our data did not show a significant association, suggesting recall bias was probably small. In fact, the odds ratio was smaller than in our previous case-control study, where family (especially maternal) history was associated with a higher odds

of trichiasis.⁴ In that study, the controls were women without scarring, suggesting that the family history of trichiasis may point to a risk factor for scarring which eventually results in trichiasis. In the current study, the controls were women with scarring, suggesting that once the scarring process has begun, the additional risk for trichiasis conferred by family history may be minimal.

A family history of trichiasis in first-degree relatives could reflect both environmental and host factors. Families could have generations exposed to repeated bouts of infection in childhood due to unsanitary conditions, child care practices, and other factors which may cluster in families over time. These families, then, would be more likely to develop trichiasis cases. Family history may also indicate a detrimental response to *C. trachomatis* ocular infection. *In vitro* and clinical studies have shown that 'prolonged' infection could be due to endogenous persistence of chlamydial organisms^{8,9} as well as repeated infections. We have shown, in prior longitudinal studies in children, that there are some children who have severe trachoma over prolonged periods of time, who maintain high chlamydial loads,^{10,11} and who seem unable to resolve infection and disease. Moreover, different immunologic responses to chlamydial infection and disease have been documented.¹²⁻¹⁴ Our semi-quantitative approach, using fluorescent units from the PCR-EIA to indicate intensity of infection, also suggest that infection in women with trichiasis is more intense compared to infection in women with no trichiasis. Such data further support differential responses to infection. Thus, family history of trichiasis could reflect the interaction of socio-environmental and immunogenetic factors that select those individuals at risk for trichiasis.

The association of chlamydial infection at follow-up, and more intense infection, with incident trichiasis is an important finding. Unfortunately, baseline infection status was not available on these women, which could establish the presence of active chlamydial infection as a risk factor for subsequent development of trichiasis. However, we have shown that active disease is a marker for infection. The presence of active disease at baseline was associated with trichiasis at follow-up, lending support to the importance of infection in the development of trichiasis. Moreover, almost all of the cases came from women with scars at baseline. The almost twofold higher infection prevalence in women with scars compared with women with no scars (and the even higher prevalence in the women who developed trichiasis) suggest that infection *per se*, whether as re-infection or persistent infection, is an important component of the pathologic process leading to trichiasis. If so, then it is important to be certain that these women are included in treatment programmes aimed at reducing active disease.

We estimate that of the 24 000 women aged 18-64 years in the Kongwa district, 21% have scars. The number of new cases of trichiasis in this group is 66 per year, with 16 new cases per year in the larger group without scars. If we presume that men have roughly the same rate of trichiasis as women without scars, then roughly 100 new cases of trichiasis in this district of 62 villages accrues each year. Severe trichiasis leads to blinding corneal damage. In a large group of trichiasis cases enrolled in a clinical trial for trichiasis surgery in Oman more than half of the eyes with central corneal opacities from trachoma were blind.¹⁵ Eye lid surgery for those with early trichiasis has been shown to be effective in correcting lid deformities in controlled trials¹⁵

and in community-based programmes.¹⁶ To prevent vision deterioration and blindness from trachoma, timely provision of surgery before the occurrence of corneal opacities is imperative. In other studies of surgical compliance in women,^{17,18} we have shown that only 27% of women in a 7-year period had sought surgical intervention to avoid blindness from trichiasis. While surgery can have beneficial effect on the current status of trichiasis, the long-term outcome among women living in hyperendemic areas where ongoing re-infection occurs is not entirely clear. In a follow-up of women who had surgery 7 years previously, the recurrence rate was 19%,¹⁶ which may have been due to constant re-exposure in this environment, leading to recurrent trichiasis.

Current World Health Organization guidelines propose a multi-faceted strategy for trachoma control that includes surgery, antibiotic use, face washing and environmental change. It is clear that for the avoidance of blindness, timely surgery for trichiasis, and antibiotic use targeted towards women with scarring are important components.

Acknowledgements

This study was funded by the Edna McConnell Clark Foundation. Dr West is Research to Prevent Blindness Senior Scientific Investigator. We gratefully acknowledge the work of Dr Virginia Turner and Mr Sidney Katala, of Helen Keller International, in assembling this original cohort.

References

- ¹Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY. Global data on blindness. *Bull WHO* 1995;**73**:115–21.
- ²West SK, Rapoza P, Muñoz B, Katala S, Taylor HR. Epidemiology of ocular chlamydia infection in a trachoma-hyperendemic area. *J Infect Dis* 1991;**163**:752–56.
- ³West SK, Muñoz B, Turner V, Mmbaga BBO, Taylor HR. The epidemiology of trachoma in Central Tanzania. *Int J Epidemiol* 1991;**20**:1088–92.
- ⁴Turner V, West SK, Muñoz B *et al*. Risk factors for trichiasis in women: a case-control study. *Int J Epidemiol* 1993;**22**:341–47.
- ⁵Thylefors B, Dawson CR, Jones BR, West SK, Taylor HR. A simple system for the assessment of trachoma and its complications. *Bull WHO* 1987;**65**:477–83.
- ⁶Taylor HR, West SK, Katala S, Foster A. Trachoma: evaluation of new grading scheme in the United Republic of Tanzania. *Bull WHO* 1987;**65**:485–88.
- ⁷Bobo L, Muñoz B, Viscidi R, Quinn T, Mkocho H, West SK. Diagnosis of chlamydia trachomatis eye infection in Tanzania by polymerase chain reaction/enzyme immunoassay. *Lancet* 1991;**338**:847–50.
- ⁸Beatty WL, Byrne GI, Morrison RP. Repeated and persistent infection with chlamydia and the development of chronic inflammation and disease. *Trends in Microbiol* 1994;**2**:94–98.
- ⁹Mabey DC, Bailey RL, Ward ME, Whittle HC. A longitudinal study of trachoma in a Gambian village: implications concerning the pathogenesis of chlamydia infection. *Epidemiol Infect* 1992;**108**:343–51.
- ¹⁰West SK, Muñoz B, Lynch M, Kayongoya A, Mmbaga BBO, Taylor HR. Risk factors for constant severe trachoma among preschool children in Kongwa, Tanzania. *Am J Epidemiol* 1996;**143**:73–78.
- ¹¹Bobo LD, Novak N, Muñoz B, Hsieh YH, Quinn TC, West SK. Severe disease in children with trachoma is associated with persistent chlamydia trachomatis infection. *J Infect Dis* 1997;**176**:1524–30.
- ¹²Holland MJ, Bailey RL, Hayes LJ, Whittle HC, Mabey DC. Conjunctival scarring in trachoma is associated with depressed cell-mediated immune responses to chlamydia antigens. *J Infect Dis* 1993;**168**:1528–31.
- ¹³Peeling RW, Bailey RL, Conway DJ *et al*. Antibody response to the 60-kDa chlamydial heat-shock protein is associated with scarring trachoma. *J Infect Dis* 1998;**177**:256–59.
- ¹⁴Bobo LD, Novak N, Mkocho H, Vitale S, West SK, Quinn TC. Evidence for a pro-inflammatory conjunctival response in individuals with trachoma. *Infect Immun* 1996;**64**:3273–79.
- ¹⁵Reacher MH, Muñoz B, Alghassany A, Daar AS, Elbualy M, Taylor HR. A controlled trial of surgery for trachomatous trichiasis of the upper lid. *Arch Ophthalmol* 1992;**110**:667–74.
- ¹⁶Bog H, Yorston D, Foster A. Results of community based eye surgery for trichiasis due to trachoma. *Br J Ophthalmol* 1993;**77**:81–83.
- ¹⁷West SK, Lynch M, Muñoz B, Katala S, Tobin S, Mmbaga BBO. Predicting surgical compliance in a cohort of women with trichiasis. *Int Ophthalmol* 1994;**18**:105–09.
- ¹⁸Oliva MS, Muñoz B, Lynch M, Mkocho H, West SK. Evaluation of barriers to surgical compliance in the treatment of trichiasis. *Int Ophthalmol* 1998;**21**:235–41.