Regression of Severe Tungiasis-Associated Morbidity after Prevention of Re-Infestation: A Case Series from Rural Madagascar

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Abstract. Tungiasis (sand flea disease) is a neglected tropical disease. Heavy infestation results in mutilation of the feet and difficulty in walking. We identified eight individuals with extremely severe tungiasis in rural Madagascar. To prevent reinfestation, four individuals received solid shoes and four received a daily application of an herbal repellent effective against *Tunga penetrans*. Over a period of 10 weeks the feet were examined and the severity of tungiasis-associated morbidity was measured. Within this period, the severity score for acute tungiasis decreased 41% in the shoe group and 89% in the repellent group. The four major inflammation-related symptoms disappeared in the four patients of the repellent group, but only in two patients of the shoe group. Those observations indicate that cases with extremely severe tungiasis, associated morbidity almost totally disappears within 10 weeks if the feet are protected by a repellent. Wearing shoes reduced acute morbidity only marginally.

INTRODUCTION

Tungiasis (sand flea disease) is a neglected tropical disease, common in South America, sub-Saharan Africa, and the Caribbean.[1,2] Sand flea disease is endemic in many resource-poor rural and urban communities.[3–9] It occurs where animal reservoirs are present and people live in poverty.[10] Usually, the poorest strata of a population are most frequently affected.[3–9,11] Ninety-nine percent of all lesions occur at the feet.[12,13] There is no effective treatment against embedded sand fleas, except a surgical extraction under sterile conditions.[2,14] People living in endemic areas do not have access to such a treatment.

In the endemic area, sand flea disease is associated with important and debilitating morbidity, such as intense inflammation around the burrowed parasites, fissures, ulcers, abscesses, and deformation of nails and toes.[5,13] If individuals are reinfested frequently, mutilation of the feet ensues, and people can hardly walk.[3,15] There is circumstantial evidence that this causes school absenteeism in children and perpetuates poverty in affected households.[15]

Because no effective drug treatment exists, the only means to prevent tungiasis-associated morbidity is to reduce the number of newly penetrating sand fleas to a negligible level. As the burrowed female sand flea dies *in situ* within 4 weeks and clinical pathology regresses when no new sand fleas penetrate, the prevention of new infestations will automatically lead to a reduction of tungiasis-associated morbidity.[16]

We have previously shown that the regular application of a repellent-based coconut oil effectively reduces tungiasis-associated morbidity in lightly and moderately infected individuals.[17–19] Here, we test the hypothesis, whether this approach is also effective in extremely severe cases and compare the effectiveness of the regular application of the repellent to the protection provided by closed shoes.

MATERIAL AND METHODS

Study area. The study was performed in the village Tanambe II (population: 507), Andasibe community, Moramanga district, Central Madagascar. Tungiasis is endemic in the village. Most of the villagers are farmers, living conditions are poor, and most individuals do not possess shoes. The social and economic characteristics of the study area have been described elsewhere.[16]

Study population and study design. When preparing an intervention study involving several communities in Moramanga district, we identified eight individuals with an extremely high intensity of infestation (more than 75 sand flea lesions). These individuals were not eligible for the intervention study, because it was impossible to exactly numerate the number of lesions and to identify the developmental stage of the embedded parasites, prerequisites for the inclusion in the clinical trial. However, we did not want to leave these individuals without attention and asked them whether they were willing to participate in a separate study.

The eight patients were permanent residents in Tanambe II. They intended to stay in their community for the next 4 months and lived in different households. The patients were randomized into two groups. The members of the first group received a pair of closed solid shoes. They were encouraged to wear the shoes whenever they walked outside. During the study period, community health workers documented the compliance by casually walking through the village once a day and noting whether the participants of this group wore their shoes or not. In the second group, Zanzarin, a repellent containing coconut oil, jojoba oil, and *Aloe vera* (Engelhard Arzneimittel GmbH & Co. KG, Niederdorfelden, Germany), was applied twice daily on the skin of both feet, up to the ankle by trained community health workers. The regular application was verified through rigid quality control.[16]

Both feet were carefully inspected for the presence of burrowed viable and non-viable sand fleas and lesions manipulated by the patient. As a result of clustering of lesions and intense inflammation, the total number of lesions could only be estimated.

The major outcome measures were the severity of acute and chronic morbidity as measured by the severity score for

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TABLE 1
Demographic and clinical characteristic of the patients at baseline

			Estimated number of lesions		Presence of			
	Age	Sex	All lesions	Manipulated lesions	Inflammation*†	Fissure*	Ulcer*	Bacterial superinfection*
Repellent group								
Patient R.R.	55	male	> 150	> 145	+++	+++	+	+++
Patient M.R.	35	female	> 75	> 55	++	++	0	0
Patient M.F.R.	13	female	> 125	> 100	+++	+	0	+++
Patient J.F.R.	8	male	> 120	> 80	+++	+++	0	+++
Shoe group								
Patient E.R.	51	female	> 140	> 128	+++	+++	+	0
Patient J.R.	19	female	> 92	> 90	++	+++	+	+
Patient Z.R.	74	female	> 85	> 82	++	+++	0	+
Patient M.R.	10	male	> 90	> 85	++	+++	++	+

*Intensity of signs was measured semi-quantitatively:
+ = sign present at 1–4 different topographic locations; ++ = sign present at 5–9 different topographic locations; +++ = sign present at > 10 different topographic locations at both feet; 0 = sign absent
†Presence of erythema, oedema, and hyperthermia.

acute tungiasis (SSAT) and the severity score for chronic tungiasis (SSCT)[20]; four major inflammation-related symptoms and signs, characteristic for tungiasis, were secondary outcome measures: pain, itching, itching- or pain-related sleep disorder, and difficulty in walking. Pain and itching were visual assessed semiquantitatively, using a visual scale (see Electronic Supplementary Material). The outcome measures were assessed every 2 weeks by the same investigator (M.T. and V.R.) for a total of 10 weeks. The study was carried out between June 16, 2011 (baseline investigation) and August 25, 2011 (final follow up). This is the period with the highest transmission of *Tunga penetrans* in Madagascar.

Statistical analysis. The median and the range were used as indicators of central tendency and dispersion of the data, respectively. The Wilcoxon–Mann–Whitney test and the Wilcoxon matched-pairs signed-rank test were used where appropriate. Two-tailed *P* values based on exact inferences were calculated (StatXact Version 9, Cytel Inc., Cambridge, MA).

Ethical considerations. The study was part of a broader project on tungiasis-associated morbidity in rural Madagascar. It was approved by the Ethical Committee of the Ministry of Health (MINSANP/CE ref.-nr. 051) and was registered at Controlled-trials.com (ISRCTN11415557). Informed written consent was obtained from all participants in Malagasy before starting the study. At the end of the study, any remaining viable sand fleas were removed under sterile conditions and all participants received a new pair of closed shoes.

RESULTS

The demographic and clinical characteristics of the patients are shown in Table 1. Patients in both groups were similar with regard to age, sex, and tungiasis-associated morbidity.

The total number of lesions (viable, dead, and manipulated lesions) was > 75 in all cases. Most lesions occurred in clusters, containing up to 30 burrowed sand fleas. The toes, the heel, and the sole were the most affected parts of the feet.

SSAT and SSCT. Figure 1 shows the time course of the severity of acute and chronic tungiasis as measured by the SSAT and SSCT. At baseline, neither the SSAT nor the SSCT were different between the shoe and the repellent group (*P* = 0.82 and *P* = 0.95, respectively). In the repellent group the SSAT already decreased after 2 weeks from a median of 17.5 to a median of 4. The SSAT continued to decrease until the end of the study (median 2). This is equivalent to a decrease

of 89% as compared with the baseline value. In the shoe group the SSAT decreased more slowly and remained high at the end of the study (baseline: median 19.5; Week 10: median 11.5). At Week 10, the SSAT was significantly lower in the repellent group than in the shoe group (*P* = 0.03). In both groups the SSCT remained almost unchanged during the study period.

Pain, itching, sleep disorder, and difficulty in walking. Table 2 depicts the evolution of four major inflammation-related symptoms and signs. At baseline, in the repellent group, two patients showed four symptoms/signs, one patient three, and one patient two. At the end of the intervention, pain, itching, sleeping disorder, and difficulty in walking had disappeared in all four patients. At baseline, in the shoe group, three patients showed four symptoms/signs and one patient one sign. However, only in two patients all symptoms/signs had disappeared at Week 10.
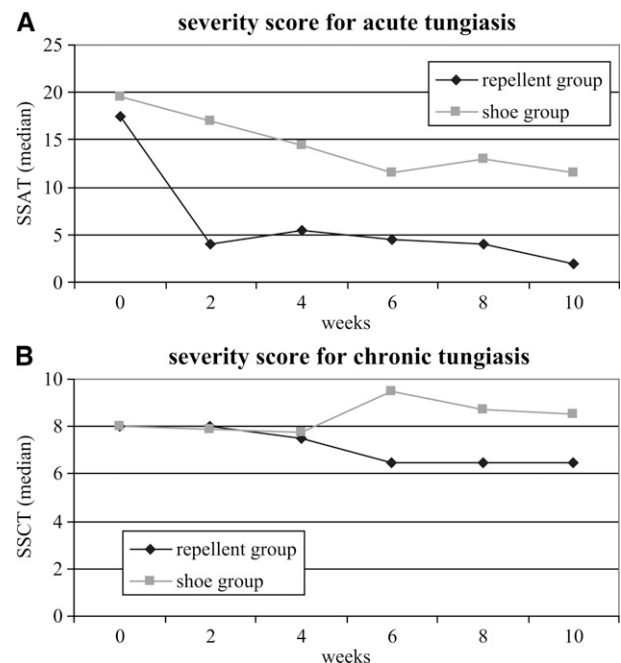

FIGURE 1. (**A**) Time course of the severity score for acute tungiasis (SSAT) (**B**) Time course of the severity score for chronic tungiasis (SSCT).

TABLE 2
Time course of major symptoms and signs

| | Baseline | | | | Week 10 | | | |
| | Intensity of | | | | Intensity of | | | |
	Spontaneous pain*	Itching*	Sleep disorder†	Difficulty in walking	Spontaneous pain*	Itching*	Sleep disorder†	Difficulty in walking
Repellent group								
Patient R.R.	4	2	Yes	Yes	0	0	No	No
Patient M.R.	0	1	Yes	No	0	0	No	No
Patient M.F.R.	3	2	Yes	Yes	0	0	No	No
Patient J.F.R.	1	0	Yes	Yes	0	0	No	No
Median; n/N	2	1.5	4/4	3/4	0	0	0/4	0/4
Shoe group								
Patient E.R.	2	2	Yes	Yes	0	0	No	No
Patient J.R.	4	4	Yes	Yes	2	2	Yes	No
Patient Z.R.	0	0	No	Yes	0	0	No	No
Patient M.R.	3	2	Yes	Yes	2	2	Yes	No
Median; n/N	2.5	2.0	3/4	4/4	1	1	2/4	0/4

* Assessed semi-quantitatively: 0 (no pain/no itching) to 4 (the worst imaginable pain/the worst imaginable itching); see Electronic Supplementary Material.
† Because of pain and/or itching.

Compliance in the shoe group. Two of the four patients, who received a pair of closed shoes at the beginning of the study, showed a good compliance: They wore their shoes in 73% and 78% of all occasions. The two other patients wore their shoes rather irregularly, namely at 44% and 55% of all occasions. Nonetheless, there was no difference between the four patients with regard to the outcome measures.

Clinical pathology. Figures 2 and 3 show a picture series of a representative patient from the repellent group and of a representative patient from the shoe group, respectively. The

FIGURE 2.   (**A**) A 55-year-old male patient from the repellent group with ~150 lesions at both feet. Most of the lesions occurred in clusters underside the toes, accompanied by deep fissures. All toes showed erythema and oedema. (**B**) The feet of the same individual after 4 weeks. At the toes, signs of inflammation have already regressed completely. The fissures are still visible. (**C**) After 6 weeks of intervention the clinical pathology has further decreased. Only some fissures still persisted. (**D**) The same patient after 10 weeks. Only residuals of lesions and fissures remained visible and the skin showed an almost normal appearance. Not a single new embedded sand flea could be seen.

FIGURE 3. (**A**) A 51-year-old patient from the shoe group with ~140 lesions at both feet. Most of the lesions occurred as clusters at the toes and the sole. They are accompanied by fissures, desquamation, erythema, and oedema. (**B**) After 4 weeks the clinical pathology has not regressed. Several ulcers are visible at the soles, the first and the forth left toe. (**C**) The same individual after 6 weeks. The clinical pathology had slightly decreased. Clusters at the sole and the fifth toe of both feet have disappeared, but new clusters have appeared at other locations. The fifth toe of the right foot is heavily inflamed. (**D**) After 10 weeks the clinical pathology remained high. Several lesion clusters still occurred at the toes and the sole of the feet, and fissures. Between both the first toes of the left and the right foot eggs of *Tunga penetrans* are being expelled.

photos taken at baseline illustrate the extremely severe clinical pathology present in the patients (Figures 2A and 3A). In the patient of the repellent group a complete resolution of clinical pathology is obvious at Week 10. At this point, the skin had an almost normal appearance (Figure 2D). In contrast, in the patient of the shoe group, tungiasis-associated inflammation of the skin partially persisted (Figure 3D).

DISCUSSION

In the endemic area tungiasis is frequently associated with important morbidity. The degree of morbidity depends on various factors, tungiasis-associated inflammation being the most important determinant.[3,5,15] As a rule, the more sand fleas that penetrate into the epidermis per unit of time, the more intense becomes the inflammation.[20,21]

In the eight patients of this case series the number of lesions was extremely high and it was impossible to exactly determine the total parasite load. By consequence, it was also impossible to determine the number of newly penetrated sand fleas between the examinations (attack rate). Hence, we could not assess to which extend the attack changed during the study period. However, serial photos of each patient showed an obvious decrease in the number of embedded parasites at

each point of follow-up, indicating that the attack rate had become zero in the repellent group. Accordingly, the severity score of acute tungiasis decreased from 19.5 points at baseline to 2 points at Week 10 in the repellent group, but only from 18 points to 12 points in the shoe group. At Week 10, the SSAT was significantly lower in the repellent than in the shoe group ($P = 0.03$). Moreover, the presence and intensity of four major sand flea disease-associated symptoms and signs changed during the observation period, reflecting a significant decrease in tungiasis-associated inflammation of the feet.

By contrast, the SSCT did not change. This is not surprising, because this score comprises signs such as nail deformation and chronic peringual oedema, which are not expected to resolve within 10 weeks.

Previous studies in Brazil showed that the plant-based repellent Zanzarin effectively prevented the penetration of sand fleas. The attack rate became zero—or near zero—immediately after the repellent had been applied to the feet regularly.[17–19] The major repellent component of Zanzarin is capric acid, a fatty acid from coconut oil. The repellent also contains jojoba oil and *Aloe vera*, which have an anti-inflammatory effect and presumably also contributed to the rapid reduction of the inflammation of the feet as soon as sand fleas were effectively repelled.

There is anecdotal evidence that wearing of closed shoes protects against invading sand fleas.[21] However, a randomized controlled study in rural Madagascar showed that the regular wearing of shoes had a significantly lower effect on the attack rate and on the regression of tungiasis-associated inflammation than the regular application of a repellent based on coconut oil when compared with a control group without intervention.[16]

Our study also shows that the availability of closed shoes does not guarantee that the shoes are worn regularly by their owners. One reason relevant to this case series is that individuals with severe tungiasis-associated morbidity refrain from wearing closed shoes, because this increases their pain.[16] Another reason is that shoes—even when a person is willing to use them—were simply not suitable all the time, such as walking or sitting inside the house, so that sand fleas could penetrate at that time.[16]

Although the number of participants of this case series was very small, it can be concluded that the twice-daily application of the repellent reduced extremely severe acute tungiasis-associated morbidity to an almost insignificant level after a couple of weeks.

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