Risk Factors for Podoconiosis: Kamwenge District, Western Uganda, September 2015

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Abstract. Podoconiosis, a noninfectious elephantiasis, is a disabling neglected tropical disease. In August 2015, an elephantiasis case-cluster was reported in Kamwenge District, western Uganda. We investigated to identify the disease's nature and risk factors. We defined a suspected podoconiosis case as onset in a Kamwenge resident of bilateral asymmetrical lower limb swelling lasting ≥ 1 month, plus ≥ 1 of the following associated symptoms: skin itching, burning sensation, plantar edema, lymph ooze, prominent skin markings, rigid toes, or mossy papillomata. A probable case was a suspected case with negative microfilaria antigen immunochromatographic card test (ruling out filarial elephantiasis). We conducted active case-finding. In a case-control investigation, we tested the hypothesis that the disease was caused by prolonged foot skin exposure to irritant soils, using 40 probable case-persons and 80 asymptomatic village control-persons, individually matched by age and sex. We collected soil samples to characterize irritants. We identified 52 suspected (including 40 probable) cases with onset from 1980 to 2015. Prevalence rates increased with age; annual incidence (by reported onset of disease) was stable over time at 2.9/100,000. We found that 93% (37/40) of cases and 68% (54/80) of controls never wore shoes at work (Mantel-Haenszel odds ratio [OR_{MH}] = 7.7; 95% [confidence interval] CI = 2.0–30); 80% (32/40) of cases and 49% (39/80) of controls never wore shoes at home (OR_{MH} = 5.2; 95% CI = 1.8–15); and 70% (27/39) of cases and 44% (35/79) of controls washed feet at day end (versus immediately after work) (OR = 11; 95% CI = 2.1–56). Soil samples were characterized as rich black-red volcanic clays. In conclusion, this reported elephantiasis is podoconiosis associated with prolonged foot exposure to volcanic soil. We recommended foot hygiene and universal use of protective shoes.

INTRODUCTION

Podoconiosis is a neglected tropical nonfilarial elephantiasis characterized by progressive bilateral asymmetrical lymphedema of the lower limbs.^{1,2} The disease is theorized to be caused by an abnormal inflammatory reaction to persistent contact with irritant volcanic soils derived from volcanic rocks. However, the exact pathogenesis is poorly understood.³ During foot contact with volcanic soils, irritant mineral particles penetrate the skin of the foot into lymphatic vessels where they are taken up by macrophages and induce inflammation with subsequent fibrosis. Recurrent exposure to irritant soils leads to repeated cycles of inflammation and fibrosis. This causes scarring and blockade of the lymphatic vessels resulting into lymphedema.³

In August 2015, the World Health Organization (WHO) Uganda Country Office received a report from a non-government organization of a perceived increase in the number of elephantiasis cases in Kamwenge District, which had caused tremendous suffering. Records showed that in 2014 a similar report was filed, which prompted the Vector Control Division, Ministry of Health of Uganda, to conduct screening for elephantiasis cases between March and April 2015 in the district. The screening ruled out lymphatic filariasis as a cause of the elephantiasis and pointed to podoconiosis. Between September 20 and 29, 2015, we conducted a formal epidemiologic investigation to confirm the diagnosis, identify risk factors for the disease, and provide evidence to guide prevention and control efforts.

METHODS AND MATERIALS

Study setting. Kamwenge District is located in western Uganda and is composed of 16 subcounties. The district's average altitude is 1,280 m above sea level and receives a well-distributed bimodal rainfall, average 1,200 mm annually.⁴ Agriculture is the main economic activity with > 90% of the population engaged in nonsubsistence maize crop farming. Twenty-four percentage of the district population fall with in the lowest two of the five quintiles on the wealth index.⁵ Our investigation was conducted in Busiriba and Kamwenge subcounties located in the northern part of the district. These subcounties were selected because they had the highest reported cases of elephantiasis. Generally in Uganda, more male-headed households (70%) own at least one pair of shoes compared with 67% in female-headed households.⁶

Study procedures. We defined a suspected podoconiosis case as onset in a Kamwenge District resident of bilateral, asymmetrical, hard swelling of lower limbs (nonpitting edema) lasting for ≥ 1 month, with history of any of the following associated symptoms from 1980 onward: lower limb skin itching, burning sensations, plantar edema, lymph ooze, prominent skin markings, hyperkeratosis (skin hardening) rigid toes, formation of mossy papillomata, or skin nodules on the lower limbs. A probable case was a suspect case with a negative microfilaria antigen on the immunochromatographic card test (ICT).^{7–9} A negative ICT result (described below under the laboratory investigation section) rules out filarial elephantiasis, thereby establishing the diagnosis of podoconiosis.¹⁰ Suspected case-patients were thoroughly examined clinically to rule out ailments such as leprosy and other skin disorders. Members of the district health team indicated that since no specific treatment of the disease is offered at the health facilities and health workers hardly understood the disease, case-persons were not

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seeking care at the district's health facilities. We therefore conducted active case-finding in affected communities using a standard questionnaire, with assistance of local health workers and authorities. During the community case-finding, we measured the altitude at which the case-patients' homes were located using a global positioning system device. We also collected soil samples from the homesteads and gardens of the cases.

We conducted a case-control investigation in the most affected subcounties to assess potential risk factors for podoconiosis transmission. Through face-to-face interviews using a standardized questionnaire, we collected information on case and control persons. We enrolled only probable case-persons for the case-control investigation. When a household had more than one case-person, we randomly selected one person to participate. For each case, we selected two controls among asymptomatic immediate neighbors to the case-persons (community controls), matched by age group (5-year age group) and sex using a case-to-control ratio of 1:2. If multiple appropriate controls were available in one household, we randomly selected one, and picked the second control from another household.

Sample size estimation. Of the 52 suspected case-persons identified by the investigating team, 40 underwent ICT and were all negative, hence meeting the definition for probable case-persons. All the 40 probable case-persons were enrolled as cases in the case-control investigation. Using the Epi Info 7 Stat calculator option for matched case-control studies, we estimated that 80 controls were needed to detect an odds ratio (OR) of 2.5 assuming the exposure rate in the nondiseased group to be 45%, with a power of 80%.

Data collection. Between September 21 and 30, 2015, we used a standardized structured questionnaire to interview cases and controls. We collected participant information on sociodemographics, including age, sex, educational level, and occupation, duration of stay in Kamwenge District, footwear, and foot hygiene practices.

Laboratory investigation. To rule out filarial elephantiasis, we obtained fingerprick blood samples from suspected case-persons and tested them for circulating *Wuchereria bancrofti* antigen using an ICT (Binax NOW® Filariasis, Inverness Medical, Scarborough, ME). Two drops of whole blood were added onto an ICT test pad and the result was subsequently observed. Although positive samples can be identified in < 5 minutes, we observed the test result after 15 minutes to maximize the test sensitivity, which peaks after this test duration. The ICT kits were refrigerated while in storage and testing strictly conducted according to the manufacturer's protocols and guidelines.⁵ The kits were kept in cool boxes throughout the fieldwork period.

Soil analysis. We collected five spot soil samples at the surface and five from a depth of 0.5 m from homesteads, gardens, and farm land areas where case-persons spent most of the time during the day. The five samples (surface and 0.5 m depth) were pooled. Two aliquots of 20 g each were preserved in 0.01% HNO₃ and subsequently 5 g of each aliquot was analyzed for free soil silicon and soil pH. The soil analysis was conducted at the Department of Chemistry Laboratory, Faculty of Science, Makerere University.

Data analysis. We assessed foot exposures to irritant volcanic soils by comparing shoe-wearing habits and foot hygiene practices between case- and control-persons. We

used the Mantel-Haenszel (MH) method to account for the matched case-control design.

Ethical considerations. The Ministry of Health of Uganda through the office of the Director General Health Services gave the directive and approval to conduct this investigation. Additionally, the office of the Associate Director for Science, Centers for Disease Control and Prevention, Uganda, determined that this investigation (protocol no. 2017-039) was not human subjects' research, because the primary purpose was to identify, characterize, and control disease in response to a perceived immediate public health threat. We obtained verbal informed consent from case-persons and controls above 18 years. For participants below 18 years of age, we sought verbal consent from their parents or guardians. We ensured privacy by conducting interviews in a secure place where none of the people around the home could follow proceedings of the interview.

RESULTS

Disease description. We identified 52 suspected case-persons with illness onset from 1980 to 2015. All suspected case-persons had a lower limb involvement (Figure 1), including lymphedema (100%), plantar edema (96%), and skin itching (94%). Genital edema was present in only one case-person. The epidemic curve showed relatively stable number of cases over the last 35 years, indicating a continuous common source exposure (Figure 2). Year of onset "heaping" of case-patients at 5-year interval was also noted. All suspected case-persons resided in 28 villages in Busiriba and Kamwenge subcounties, located in the northern part of the district (at-risk population = 421,470). These subcounties are at a high altitude (median = 1,263 m; range = 1,163–1,328 m) (Figure 3). The annual disease incidence based on the suspected cases was 2.9/100,000. The mean age of the suspected cases was 48 (range = 13–80) years. The prevalence rate increased with age (Table 1). The median age of disease onset (lower limb swelling) was 35 (range = 8–76) years. Females had a higher attack rate (1.6/1,000) than males (0.32/1,000).

Hypothesis generation. Interview of 24 initial case-persons revealed that all were farmers engaged in digging and growing various crops; 14 (63%) never wore shoes while at work and 16 (67%) never washed their feet during the day and only washed feet before going to bed to sleep. We therefore hypothesized that the disease was associated to prolonged exposure to volcanic soils. Findings of the case-control investigation were as follows: in the case-control investigation, not wearing shoes at work was associated with being a case (MH OR(OR_{MH}) = 7.7; 95% confidence interval [CI] = 2.0–30) and so was not wearing shoes at home (OR_{MH} = 5.2; 95% CI = 1.8–15), as shown in Table 2. When we cross-tabulated shoe-wearing behaviors at work and at home, not wearing shoes at work nor at home was more associated with being a case compared with wearing shoes both at work and at home (OR_{MH} = 13; 95% CI = 2.6–61) (Table 3). Similarly, only washing feet at the end of the day before going to bed to sleep (compared with washing feet within 2 hours after returning home from the fields) was more associated with being a case (OR_{MH} = 11; 95% CI = 2.0–56) (Table 3). The type, structure, or cover of the floor at the participants' homes or kitchen, and cultivating activities

FIGURE 1. Clinical manifestations of podoconiosis in selected case-persons: Kamwenge District, Uganda, 1980–2015. Pictures were taken with consent from the participants during the investigation.

in valley areas or cultivating activities in the areas adjacent to the Kibaale Forest were not associated with the disease.

We also observed disease clustering within families: 55% of case-persons compared with 15% of controls reported a similar illness in at least one family member ($OR_{MH} = 11$; 95% CI = 3.3–42). Compared with not having any family member with similar disease or disease in a non blood relative family member, persons having a blood relative with

podoconiosis were more likely to be a case ($OR_{MH} = 9.2$; 95% CI = 2.0–44).

Soil analysis. Of the 20 soil samples tested, the mean free Silicon was 14 mg/dL (8.7–18 mg/dL). The average pH was 6.3 (range = 5.6–6.8), which is in the acidic range.

DISCUSSION

Our investigation has uncovered endemic of elephantiasis that was clinically and epidemiologically consistent with podoconiosis in Kamwenge District, an area that has not previously been known to be endemic for this disease. The investigation demonstrated that simple and inexpensive interventions to prevent foot exposure to irritant soils, such as improving basic foot hygiene and ensuring universal use of protective foot wear, can go a long way in preventing this debilitating disease.

Podoconiosis is nonfilarial elephantiasis mainly affecting lower limbs bilaterally. Typically, podoconiosis presents with bilateral asymmetrical lower limb lymphedema that rarely involves the genitals or progresses above the knee, preceded by repeated episodes of itching of the skin of the forefoot and with associated burning sensations.^{11–15} The disease has been associated with prolonged exposure to irritant alkaline soils derived from the alkaline rock.^{12,13}

FIGURE 2. Year of onset of podoconiosis cases: Kamwenge District, Uganda, 1980–2015.

Geographic distribution of Podoconiosis cases in Kamwenge district

FIGURE 3. Geographical concentration of podoconiosis case-persons in Kamwenge and Busiriba subcounties: Kamwenge District, Uganda, 1980–2015.

Podoconiosis is associated with high levels of disability, reduced productivity, and social stigma. The disease, however, is totally preventable with simple basic interventions.^{16,17} Contrary to the perception that an outbreak of elephantiasis had occurred in the area, we have uncovered a chronic neglected tropical disease with a relatively stable annual incidence over the last three decades. The year on onset “heaping” at 5-year intervals noted on the epidemic curve could be due to problems with recalling events that

happened > 20 years back. The fact that this disease had never before been reported in this remote area implies that the residents have been silently suffering from this disease without help for more than 30 years.

Globally, it is estimated that about 4 million people are affected by podoconiosis, particularly in east and central Africa, Central and South America, and southeast Asia.^{13,14,18–21} Surveys have noted a prevalence of 5–10% among populations who work barefooted on irritant soils in endemic areas.²² High prevalence of podoconiosis has been found in countries such as Ethiopia, India, Uganda, and Cameroon.^{22–27} In Uganda, the disease has been reported on the slopes of Mt Elgon in Kapchorwa in northeastern Uganda (areas rich in volcanic soils), and in the highlands of Kabale and Kisoro districts in southwestern Uganda.^{1,22,28,29} However, podoconiosis had never before been recognized in western Uganda (Toro–Ankole region).

In this investigation, women were at greater risk compared with men. Most of the published studies have shown a higher risk in women as well.^{12,23,24,30,31} The few exceptions were in central Ethiopia, the male-to-female ratio was 1.2:1²⁵ and in a previous study in eastern Uganda, the male-to-female ratio was 1:1.²² The exact reason that women had a higher risk was unknown. In our investigation, the higher risk among women might be due to the fact that, in rural Uganda, women are more likely than men to be engaged in

TABLE 1

Prevalence rate of podoconiosis by sex, subcounty of residence, and age: Kamwenge District, Uganda, 1980–2015

Case-person characteristics	No. of suspected case-persons	Total population	Prevalence rate/1,000
Total	52	51,553	1.0
Sex			
Female	44	26,840	1.6
Male	8	36,712	0.22
Subcounty			
Busiriba	37	28,596	1.3
Kamwenge	15	22,957	0.65
Age group (years)			
13–20	4	5,797	0.69
21–30	3	3,896	0.77
31–60	30	5,263	5.7
60–100	15	938	16

TABLE 2
Risk factors for podoconiosis: Kamwenge District, Uganda, 1980–2015

Risk factor	% Exposed		Adjusted Mantel–Haenszel odds ratio (95% confidence interval)
	Cases (N = 40)	Controls (N = 80)	
Wearing shoes at work			
No	93	68	7.7 (2.0–30)
Yes	7	32	Reference
Wearing shoes at home			
No	80	49	5.2 (1.8–15)
Yes	20	51	Reference
Similar disease in family member			
Yes	55	15	11 (3.3–42)
No	45	85	Reference
Washing feet			
At end of day (> 4 hours after work)	69	35	11 (2.0–56)
2–4 hours after work	21	20	4.9 (0.91–26)
< 2 hours after work	10	45	Reference

agriculture activities and spend longer periods in the fields and are therefore more exposed to irritant soils.⁴ This can also be explained by sex differences in preventive behaviors such as shoe ownership and shoe use between men and women.

Podoconiosis has been theorized to be caused by an interplay between environmental risk and personal factors that predispose an individual to prolonged exposure with irritant volcanic soils.^{13,32–35} Our investigation findings were consistent with findings of previous studies that showed that podoconiosis generally occurred in high-altitude and high-precipitation (> 1,000 mm annually) areas.³⁶ Kamwenge District and surrounding districts are known to have heavy annual precipitation of 1,200 mm.³⁷ The low pH (measure of solvated hydrogen ion to define acidity or alkalinity) of the soils in the area was similar to that documented elsewhere and has been mainly attributed to the high rainfall, leaching calcium and other bases in the volcanic soils.³⁶ The Toro–Ankole volcanics where Kamwenge District is located lies in the western branch of the East African Rift System.³⁸ Geochronological data suggest that about 2.5 million years ago during the late quaternary pulse of volcanic activity that occurred in the area, emitted alkaline magma rocks and ashes, which have undergone chemical weathering over time.^{39–42} The soils in the area are predominantly cambisols and ferralsols with weathered volcanic nitiosols on the gentle slopes plus clay-rich vertisols in the valley floors. Such soils also exist in some parts in eastern and northwestern Uganda (West Nile).⁴³ However, the area where the disease was reported was once covered by extensive forest and grassland vegetation. However, beginning in the 1960s, massive migration of mainly cultivators from southwest Uganda replaced the indigenous hunter-gathering tribe of the area and, subsequently, the soils were laid bare.^{37,44} This period of mass cultivation coincides with the appearance of the disease in the area.

Our findings also showed that, whereas both case-persons and controls were predominantly farmers, not wearing shoes at work or at home was strongly associated with developing podoconiosis. In addition, quickly washing feet after soil exposure was protective against disease risk. This finding was consistent with those in previous studies conducted in Ethiopia.^{20,30,32,45} Unlike in previous studies, our investigation found no association between the floor type or floor cover in the house and disease. This lack of association could be explained by the fact that these floor covers were partial and do not prevent feet–soil contact. The floor covers in the area were mainly for people to sit, particularly during meal times.

Podoconiosis has been noted in the published literature to have a genetic predisposition, with family clustering of the disease noted in Rwanda, Ethiopia, and Burundi.^{30,33} A study by Davey and others in Ethiopia found a 5-fold increase in podoconiosis risk among siblings of affected individuals.³⁴ Our investigation found a 9-fold increase in the odds of disease development among participants with history of disease among family members. However, this association became statistically nonsignificant on stratification on blood relations, indicating that the association was due to confounding.

In this investigation, due to logistical challenges, we were only able to take 20 soil samples for analysis. We were also unable to histologically rule out other pathologies such as leprosy or Kaposi sarcoma, which might lead to misclassification of podoconiosis.¹⁵ However, in making a podoconiosis diagnosis, WHO recommends consideration of one's location, history, clinical findings, and absence of microfilaria or antigen on immunological card test in populations living at high altitudes (> 1000 m above the sea level). More still, the ICT has been shown to be an appropriate field test for detecting microfilaria with > 95% sensitivity and 100%

TABLE 3
Stratified analysis on not wearing of shoes as a risk factor for podoconiosis: Kamwenge, Uganda, 1980–2015

Wearing shoes at work	Wearing shoes at home	% Exposed		Adjusted Mantel–Haenszel odds ratio (95% confidence interval)
		Cases (N = 40)	Controls (N = 80)	
No	No	78	46	13 (2.6–61)
Yes	No	15	21	3.6 (0.62–21)
No	Yes	2.5	2.5	5.4 (0.31–95)
Yes	Yes	5	30	Reference

specificity when compared with thick blood smear examination.^{7–9,46} We strictly adhered to the WHO gold standard for podoconiosis diagnosis.⁴⁷ Further still, studies have shown that the negative predictive value of using a mere clinical assessment in making a podoconiosis diagnosis exceeds 90%, compared with the WHO gold standard.⁴⁸

In conclusion, our investigation revealed nonfilarial elephantiasis consistent with podoconiosis in an area not previously known to be endemic with this disease. Prolonged foot exposure to irritant volcanic soils (as a result of not wearing protective foot wear while at work and home and delayed foot washing to get rid of irritant soils) was strongly associated with the disease. We recommend that residents in Kamwenge District are provided with gumboots or other protective shoes to reduce the risk of this disabling disease. Our study findings served to inform the Ugandan Ministry of Health and Kamwenge District local government about the existence of podoconiosis in the region and as a basis for advocacy and programming. Surveillance and provision of care for patients with podoconiosis ensued following dissemination of the study findings. Further research to better understand the genetic dynamics of the disease in the country is commended.

Received November 28, 2016. Accepted for publication February 19, 2017.

Published online April 10, 2017.

Acknowledgments: We would like to acknowledge the Kamwenge District leadership for mobilizing the communities during this investigation. Their guidance and coordination made field work and data collection possible. We also acknowledge the personnel at Department of Chemistry, Faculty of Science, Makerere University for their contribution to this work. The American Society of Tropical Medicine and Hygiene (ASTMH) assisted with publication expenses.

Financial support: This investigation was financially supported by the World Health Organization, Uganda Office. Christine Kihembo and Ben Masiira are fellows of the Uganda Public Health Fellowship Program, Field Epidemiology Track, financially and technically supported by the U.S. Centers for Diseases Control and Prevention.

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