

Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans

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Hookworm-related cutaneous larva migrans is caused by the migration of animal hookworm larvae in the human skin. The disease mainly occurs in resource-poor communities in the developing world, but it is also reported sporadically in high-income countries and in tourists who have visited the tropics. Diagnosis is made clinically in the presence of a linear serpiginous track moving forward in the skin, associated with itching and a history of exposure. Itching is typically very intense and can prevent patients from sleeping. Bacterial superinfection occurs as a result of scratching. Treatment is based on oral drugs (albendazole or ivermectin) or the topical application of tiabendazole. To control hookworm-related cutaneous larva migrans at the community level, regular treatment of dogs and cats with anthelmintic drugs is necessary, but this is seldom feasible in resource-poor settings. Animals should be banned from beaches and playgrounds. For protection at the individual level, unprotected skin should not come into contact with possibly contaminated soil.

Introduction

In 1874, Lee¹ described for the first time a “creeping eruption” on the skin of a patient. About 50 years later, Kirby-Smith and colleagues² discovered a nematode larva in the skin biopsy sample of a patient with a creeping eruption. In the following years, experimental infections of volunteers with larvae of the dog and cat hookworms *Ancylostoma braziliense*, *Ancylostoma caninum*, and *Uncinaria stenocephala* consistently produced the clinical sign of a creeping eruption.^{3–7}

For decades, the terms cutaneous larva migrans and creeping eruption have been used as synonyms. The first term describes a syndrome and the second a clinical sign, present in a variety of conditions.^{8–10} A creeping eruption is defined clinically as a linear or serpiginous, slightly elevated, erythematous track that moves forward in an irregular pattern (figure 1).^{9,11} It can be caused by animal hookworm and other nematode larvae, or by parasites such as *Gnathostoma* spp and *Loa loa*,^{8,9,12–15} *Sarcoptes scabiei* (scabies mites), and larvae of parasitic flies (migratory myiasis).

A creeping eruption caused by *Strongyloides stercoralis* is called larva currens. The term reflects the fast movement

of strongyloides larvae. Recently, the trematode *Fasciola gigantica* and the nematode *Spirurina* spp have been identified as rare causes for creeping eruption in Vietnam and Japan, respectively.^{16,17}

Obviously, the syndrome cutaneous larva migrans excludes conditions in which the creeping eruption is caused by non-larval forms of migratory parasites, such as in dracontiasis, loiasis, or scabies, or when larvae penetrate the dermis, with or without producing the clinical picture of a creeping eruption. This is the case in cercarial dermatitis (schistosomiasis), onchocerciasis, and dirofilariasis.^{8,9,18}

When animal hookworm larvae are responsible for a creeping eruption, the disease is called hookworm-related cutaneous larva migrans.^{8,9} We describe the epidemiological and clinical characteristics of this condition, which causes substantial discomfort to several millions of people in developing countries every year.

Biology

Adult hookworms live in the intestine of dogs and cats. Infection may be asymptomatic in these animals, but it can cause wasting, anaemia, and death.¹⁹ Eggs shed in faeces hatch in the superficial layer of the soil within 1 day, and develop into infective third-stage larvae after about 1 week.^{5,11} When larvae are protected from direct sunlight and desiccation in a warm and humid environment, they can survive and remain infective for several months.

Third-stage *A caninum* larvae respond to soil vibration and increases in temperature with snake-like movements.²⁰ The characteristic movement seems to help the larvae find an animal host. This waving behaviour is also stimulated by the carbon dioxide content of the air.²⁰

Similar to human hookworm larvae, host-seeking in *A caninum* larvae is driven by a temperature gradient.^{20–22} After having located a host, larvae creep on the skin surface investigating a suitable penetration site.²³ Eventually, the larvae penetrate into the corneal layer of the epidermis.^{19,24–27} The infective third-stage larvae excrete a protease and a hyaluronidase, enabling passage through the skin.²⁸



Figure 1: Characteristic creeping eruption in a child with hookworm-related cutaneous larva migrans

In the animal host, larvae penetrate into the lymphatic and venous system, eventually causing intestinal hookworm disease. However, in human beings, larvae cannot penetrate further and are confined to the skin, where they are unable to develop and complete their lifecycle, as they would do in dogs and cats.^{29,30} Thus, human beings are accidental hosts and a parasitological impasse. By consequence, hookworm-related cutaneous larva migrans is a self-limiting disease that can persist for months, and rarely for years.^{10,24,31–35}

Depending on the hookworm species, larvae migrate some millimetres up to a few centimetres per day. Sandground³⁶ observed itching within 1 h after participants were infested with a single *A. braziliense* larva, whereas the creeping eruption became visible only after a few days. By contrast, in experimental infestation with *U. stenocephala*, papules developed after 4–6 days, and a track appeared after 2 weeks.⁷ Jackson and colleagues³⁷ estimated, based on the duration of infestations and the length of tracks, an average prolongation of the creeping eruption of 2.7 mm per day; however, the hookworm species was not determined in this study.

Geographical distribution and seasonal variation

Hookworm-related cutaneous larva migrans is endemic in resource-poor communities in the developing world, particularly in Brazil, India, and the West Indies.^{37–40} The disease occurs sporadically or in the form of small epidemics in high-income countries and is reported in tourists who have visited the tropics. The infestation is frequent in areas where stray dogs and cats are common or where pets are not treated regularly with anthelmintics.

There is a distinct seasonal variation of hookworm-related cutaneous larva migrans, with a peak incidence during the rainy season.^{41,42} Embryonated eggs and larvae survive longer in wet soil than in dry soil and are dispersed over a wide area by heavy rainfalls. By consequence, the risk of desiccation of eggs and larvae is much higher in the dry season than the rainy season. Additionally, a wet climate leads also to an increase of hookworm disease in dogs and cats, which in turn will augment the dispersion of contaminated faeces and the risk of infection in human beings.

Clinical picture

Usually, itching begins shortly after larvae have started to penetrate into the epidermis. A reddish papule appears at the penetration site in immunologically naive individuals and also in individuals sensitised previously. Hence, the itchy sensation does not reflect a specific immune response, but seems to be triggered by stimulation of itching fibres, presumably by substances released from the larva. In most cases, 1–5 days after penetration the elevated track appears (figure 1). However,



Figure 2: Bullous lesions in a patient with hookworm-related cutaneous larva migrans

studies on travellers have shown that the incubation period may last a month or even longer.^{10,33,43} Larvae usually migrate in the epidermis for 2–8 weeks to several months.^{10,24,31,33,37} The itching is intense and described as very uncomfortable by patients.^{37,39} A recent study showed that 81% of patients with hookworm-related cutaneous larva migrans were prevented from normal sleep because of the intensity of itching.³⁷ Pain can also be present.^{37,39}

Lesions tend to become superinfected with pathogenic bacteria as a result of scratching, particularly in developing countries.^{30,39,41,44} In resource-poor communities in Brazil, superinfection of lesions was observed in 8–24% of patients,^{37,39} whereas superinfection in returning travellers with hookworm-related cutaneous larva migrans occurred in 0–8%.^{10,24,43} *Staphylococcus aureus* and streptococci are particularly common causes of superinfection of lesions. If lesions remain infected with group A streptococci for a prolonged period of time, post-streptococcal glomerulonephritis may ensue.⁴⁵

Vesiculobullous lesions (figure 2) occur in 9–15% of cases,^{26,31} with bullae sometimes reaching an impressive size of several centimetres.⁴⁶ The pathophysiology of bulla formation in hookworm-related cutaneous larva migrans is not known. Folliculitis (the presence of a papulopustular inflammation of follicles) is an uncommon clinical manifestation of hookworm-related cutaneous larva migrans and has been described in travellers returning from tropical countries.^{31,47,48} Erythema multiforme is seen sporadically, and is considered a complication in previously sensitised individuals.⁴⁹ Very rarely, animal hookworm larvae may invade the viscera and cause pulmonary eosinophilia (Loeffler's syndrome).^{50–52} *A. caninum* infection can cause eosinophilic enteritis,⁵³ characterised by abdominal pain associated with nausea and diarrhoea. The condition may mimic acute appendicitis or intestinal obstruction.^{15,53}

In massive infestation, larval invasion of skeletal muscles has been described. Little and colleagues⁵⁴

diagnosed hookworm-related cutaneous larva migrans in a man who had crawled under a house in Louisiana, USA, and developed intense itching a few hours later. The next day, multiple creeping eruptions appeared, and he developed pulmonary symptoms. Pulmonary infiltrates persisted for weeks. 3 months after infestation, an ancylostoma larva (probably *A. caninum*), was detected in a biopsy sample of skeletal muscle.⁵⁴

Most patients have only a single larval track. If several tracks are present, they may occur at different topographic sites. Lesions are usually located on the feet, buttocks, and thighs—ie, parts of unprotected skin that come into contact with contaminated soil. Tracks are also regularly found on the arms, elbows, legs, knees, and back,^{24,33,37,39} and can occur on any area of the body including the face, scalp, and genitals.^{24,41,55–59} Lesions have even been reported on the oral mucosa^{60,61} or within sebaceous glands on the scalp.⁵⁹ These rare localisations are explained by the creeping of larvae on the skin before penetration. Alternatively, larvae may be transferred to human skin through contaminated clothes, towels, or other objects.

In endemic areas, the topographic distribution of tracks varies according to age; children have more lesions on the buttocks, genitals, and hands, whereas lesions in adults are almost exclusively found on the legs and feet.³⁷

The topographic distribution of lesions in tourists differs from that found in people living in endemic communities. In a study of people living in an urban slum in an endemic area, most tracks occurred on the trunk and the legs, and not a single track was found on the feet.³⁹ By contrast, in tourists, the feet, buttocks, and thighs—body areas that typically come into contact with contaminated sand while walking or sitting on the beach—are affected in decreasing order of frequency.^{24,26,31,33,43,62} In India, a massive infestation with innumerable lesions on the scalp, face, trunk, and arms was reported in a man sleeping on the wet floor of a bus station.⁶³

Infestation through contaminated fomites is rare. In Italy a small outbreak of hookworm-related cutaneous larva migrans was reported involving six individuals with lesions on the anterior part of thighs, arms, and chest, caused by contaminated dried flowers used for decoration purposes.⁶⁴

Diagnosis and differential diagnosis

The diagnosis of hookworm-related cutaneous larva migrans is easily made clinically and is supported by a travel history, or in an endemic setting, by possibility of exposure.^{10,11,26,30,65,66} Creeping eruption as a clinical sign is diagnostic; a biopsy is not useful. The invasive procedure only rarely identifies the parasites, since the anterior end of the track does not necessarily indicate the place where the larva is located.

Eosinophilia may or may not be present and is not specific.^{24,33,67} In a study in Germany on returning travellers with hookworm-related cutaneous larva

migrans, only eight (20%) of 40 presented with eosinophilia, but infection status regarding other helminths was not known.³³ However, a high eosinophil count can indicate migration of helminth larvae into the viscera, a rare complication.

Cutaneous larva migrans caused by *A. caninum* may be detected by ELISA. The test has been applied in a single case, and there are no data on sensitivity and specificity.⁶⁸ Recently, epiluminescence microscopy has been used to visualise migrating larvae.^{69,70} The sensitivity of this method is not known.

For clinicians not familiar with hookworm-related cutaneous larva migrans, the disease may mimic scabies, loiasis, myiasis, cercarial dermatitis (schistosomiasis), tinea corporis, and contact dermatitis, but considering the characteristic features of hookworm-related cutaneous larva migrans, these conditions are ruled out easily.^{10,11} Larva currens has to be excluded. *S. stercoralis* larvae migrate several centimetres per hour, considerably faster than those of animal hookworms and the track moves forward in a haphazard manner; lesions persist for only a few hours and occur in the perianal area, on the thighs, and on the trunk.^{30,71}

Hookworm-related cutaneous larva migrans can mimic herpes zoster;⁷² however, the latter follows the anatomic path of a peripheral nerve and does not progress in the manner that the creeping eruption in hookworm-related cutaneous larva migrans does. A serpiginous ganglion cyst has also to be considered as a differential diagnosis.⁷³ Another condition of non-parasitic origin resembling creeping eruption has been a hair growing horizontally in the skin.⁷⁴

Case management

Oral treatment

Three drugs are available for systemic treatment, all of which are powerful anthelmintics.^{75–78} The drug of choice is ivermectin. A single dose (200 µg per kg bodyweight) kills the migrating larvae effectively and relieves itching quickly.^{75,79–81} Cure rates after a single dose range from 77% to 100%.^{31,43,79,82} In the event of treatment failure, a second dose usually provides a definitive cure.^{43,75,82} Repeated treatment may be necessary in hookworm folliculitis.⁴⁸ Ivermectin is contraindicated in children who weigh less than 15 kg (or are less than 5 years of age) and in pregnant or breastfeeding women. However, off-label treatment of children and inadvertent treatment of pregnant women have occurred without reports of significant adverse events.^{83,84} Ivermectin has an excellent safety profile, and has been used in millions of individuals in the developing world during onchocerciasis and filariasis control operations without any notable adverse events.⁸⁵

A single dose of ivermectin is more effective than a single dose of albendazole,^{24,75,79} but repeated treatments with albendazole are a good alternative in countries where ivermectin is not available. Oral albendazole (400 mg daily), given for 5–7 days, showed excellent cure rates of

92–100%, and the drug is well-tolerated by patients.^{75,77,78,86,87} Because a single dose of albendazole has a lower efficacy,⁷⁵ a 3-day regimen of albendazole is usually recommended.¹⁰ An alternative approach is to start with a first dose of albendazole and to repeat the treatment if necessary.

Tiabendazole (50 mg per kg bodyweight for 2–4 days) was widely used after the first report of its efficacy in 1963.^{88–94} However, given orally the substance is poorly tolerated, and frequently causes dizziness, nausea, vomiting, and intestinal cramps.^{24,75,89,92} Since ivermectin and albendazole perform better and cause fewer adverse events, the use of oral tiabendazole is not recommended.

Topical treatment

Topical tiabendazole has been used for more than 40 years.^{93,95–98} Topical application on lesions in a concentration of 10–15% three times daily for 5–7 days is as effective as oral treatment with ivermectin.^{26,33,99} The topical treatment is without adverse events, but requires good compliance from the patient. Topical tiabendazole is of limited value in the presence of multiple or widespread lesions, and is not effective in hookworm folliculitis.⁷⁵

Ivermectin and albendazole are promising compounds for topical use, especially in children, but efficacy data on this form of administration are limited.¹⁰⁰

Freezing the edge of the track with liquid nitrogen or carbon dioxide is obsolete, since it is ineffective, painful, and may cause ulcerations.^{26,75,101} Secondary infections should be treated with a topical antibiotic.

Hookworm-related cutaneous larva migrans in low-income settings

In rural areas in South Africa, China, and Argentina, and also in urban areas in Uruguay and Netherlands Antilles, the prevalence of *Ancylostoma* spp in dogs ranges from 66% to 96%.^{102–107} Backyards, streets, public parks, and playgrounds are frequently contaminated by dog and cat faeces, and hookworm larvae are commonly found in soil samples from such places.^{108–111} Sand samples from a Caribbean beach have contained hookworm larvae of animal origin.¹¹² As a result, outbreaks have been reported in kindergartens, schools, public parks, and in children playing in sand boxes.^{44,110,113–115}

In many resource-poor communities in the tropics, people walk barefooted, children crawl or sit naked on the ground, and pet animals are frequently infected with hookworms; therefore, the prevalence of hookworm-related cutaneous larva migrans is expected to be high. For instance, in urban slums and rural communities in Brazil up to 4% of the general population and 15% of children can be infested.^{41,42} A low socioeconomic status and certain behaviour, such as walking barefoot, were identified as risk factors for the presence of hookworm-related cutaneous larva migrans in this setting.⁴²



Figure 3: Sign prohibiting dogs to be taken to the beach in Mallorca, Spain

In low-income settings, people regard hookworm-related cutaneous larva migrans as a nuisance, and many are affected by the parasitic skin disease.^{37,116} Treatment is often not available at local health-care centres and needs to be purchased at the pharmacy.

Hookworm-related cutaneous larva migrans in high-income countries

Sporadic cases of autochthonous hookworm-related cutaneous larva migrans acquired in high-income countries of temperate climate are usually associated with untypical climatic conditions, such as prolonged periods of warm weather and rainfall. Such cases have been reported in Germany, France, UK, New Zealand, and northern Australia.^{117–127} When people live in close contact with their pets, infestations can also occur in winter time.¹²²

In high-income countries with hot climates, such as in the southern USA, hookworm-related cutaneous larva migrans occurs sporadically or in small epidemics.^{117,128–133} A study in Florida between 1998 and 2000 found that 20 (33%) of 60 feral cats were infected with *A. braziliense*.¹³⁴ In Italy, an outbreak has been reported, and autochthonous cases have occurred, in beach volley ball and beach soccer players.^{55,135,136}

If the global temperature increases further during the next decades, the occurrence of hookworm-related cutaneous larva migrans in high-income countries is expected to increase.

Hookworm-related cutaneous larva migrans in travellers

Most patients with hookworm-related cutaneous larva migrans seen by health-care professionals in high-income countries are travellers returning from the tropics and

subtropics.^{11,26,31,33,43,137–142} A study based on 30 GeoSentinel sites including more than 17 000 travellers who returned ill showed that hookworm-related cutaneous larva migrans occurred in 2–3% of them, with the highest prevalence of the condition in those returning from Caribbean destinations, followed by southeast Asia, and Central America.¹⁴⁰ Similarly, in French travellers returning from tropical destinations who presented at a tropical diseases unit in Paris, hookworm-related cutaneous larva migrans was diagnosed in eight (1.3%) of 622 patients.¹³⁸

At specialised units, the occurrence of hookworm-related cutaneous larva migrans is even higher. In three Italian dermatology clinics, 78 (70%) of 111 diagnosed parasitic conditions in travellers were hookworm-related cutaneous larva migrans,¹³⁹ and the disease was confirmed in 25% of 269 patients presenting with dermatoses during a 2-year period in a tropical disease unit in France.³¹ Of 1010 returning travellers diagnosed with a parasitic condition at a tropical disease unit in Toronto (ON, Canada), 105 (10.4%) were diagnosed with hookworm-related cutaneous larva migrans, 92% of whom were tourists.¹⁴² The high frequency of hookworm-related cutaneous larva migrans in tourists compared with other travellers (such as business travellers and people visiting friends and relatives) was confirmed in studies from France and Canada.^{142,143} The Canadian study found that the disease in tourists was mainly acquired from beach destinations in Jamaica, Barbados, Brazil, Thailand, and Mexico.¹⁴² An outbreak of hookworm-related cutaneous larva migrans in military personnel has been reported in Belize.¹⁴⁴

Tourists are often not aware of the risk for acquiring hookworm-related cutaneous larva migrans when walking barefoot on beaches, or when sunbathing on the beach. Thus, the fact that most cases in tourists are acquired on tropical beach destinations reflects a typical risk behaviour of tourists rather than the true distribution of hookworm larvae in the endemic area. A recent airport-based study on international travellers leaving northeast Brazil showed that all travellers who acquired hookworm-related cutaneous larva migrans during their stay had visited beaches.¹⁴⁵ Protective footwear—eg, wearing sandals to the beach and on the beach—has shown to be effective in reducing infestation.⁶²

Prevention and control

Human beings have kept domesticated dogs and cats since prehistoric times, and the close bond between human beings and domestic animals has facilitated the spread of zoonotic infections throughout the world.¹⁴⁶ Still today, human attitudes towards dogs and cats have a crucial role in the spread of zoonotic diseases. The dog population in areas endemic for hookworm-related cutaneous larva migrans is diverse and includes owned

dogs (pet dogs) with restricted movement, free-ranging dogs that may receive some shelter or food from human beings but that are not owned, and feral dogs.¹⁴⁶ Free-ranging and feral dogs account for about half of the dog population in developing countries.¹⁴⁶ The situation is similar for cats.

To control hookworm-related cutaneous larva migrans at the community level, dogs and cats have to be treated regularly with anthelmintic drugs. However, in resource-poor communities, control is made difficult by financial constraints, the high number of stray dogs and cats, a deficient public veterinary health system, and unawareness of health risks by pet holders.²⁷ It is clear that in these settings, control can only be achieved by an integrated approach, based on cooperation between public-health professionals, medical anthropologists, veterinarians, and the community.²⁷

Control based on health education and community participation in treatment of the animal reservoir have been effective and efficient in an endemic area in South Africa, where the number of cases decreased from 15 per month to none after applying these strategies.¹⁴⁷ Health education should be focused on mothers and teenage girls who take care of their younger siblings, since most cases in low-income communities occur in infants, toddlers, and small children.⁴²

In high-income countries, pets should be dewormed regularly. In urban areas animals should be banned from beaches and playgrounds, and faeces should be collected by the pet owner immediately after defecation.

Sand pits should be covered with clear plastic covers to prevent animals defecating in them at night.¹⁴⁸ It has also been postulated that this control measure would result in high soil temperature during daily sunlight, preventing survival of larvae.¹⁴⁸

The only means of prevention at the individual level in endemic areas is to avoid unprotected skin coming into contact with possibly contaminated soil. However, such behavioural changes are difficult to encourage, since they are deeply rooted in a societal context. Besides, families in low-income endemic areas are often too poor to afford shoes for all children.

Tourists should be advised to use sandals when walking on the beach, to avoid beaches where dogs and cats stroll around, and to use a sun chair on tropical beaches.^{11,62} Lying on towels does not protect sufficiently. Areas on the beach where the sand has been humidified by the tide can be considered as safe. Additionally, animals should be banned from beaches (figure 3). Towels and clothes should not touch the ground when hung up for drying. In general, tourists should avoid direct soil contact in places where dogs and cats are observed.

Conclusion

Hookworm-related cutaneous larva migrans occurs in endemic areas mainly in low-income communities, but also in tourists visiting beach destinations in tropical and

Search strategy and selection criteria

Data for this Review were found through searches of Medline, Lilacs, and Cochrane databases using the keywords "cutaneous larva migrans", "creeping eruption", and "parasitic skin disease". Additionally, reference lists of retrieved articles were searched for further studies. No date restrictions were set in these searches, but when selecting articles, emphasis was given to papers published in the past 15 years. Articles in English, French, German, Spanish, Portuguese, and Italian were analysed. References found in text books on dermatology, parasitic diseases, and tropical medicine were also used.

subtropical areas. The disease causes discomfort and substantial morbidity. Adequate prevention measures using an integrative approach need to be implemented to reduce the occurrence of hookworm-related cutaneous larva migrans.

Conflicts of interest

We declare that we have no conflicts of interest.

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