

PODOCONIOSIS, NON-FILARIAL ELEPHANTIASIS, AND LYMPHOLOGY

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ABSTRACT

Several recent reviews of podoconiosis already exist in journals and on public access websites. After briefly covering the historical and epidemiological background, this narrative review will therefore attempt explicitly to link podoconiosis with lymphology, examining gaps in what is known of pathogenesis and identifying the areas of research in which input from lymphologists is most required. Finally, prevention and treatment will be described and the need for operational research to optimize community-based interventions outlined.

Keywords: podoconiosis, elephantiasis, lymphedema, soil

Podoconiosis is a type of lower limb tropical elephantiasis distinct from lymphatic filariasis (LF). It is a geographically localized disease, clinically distinguished from LF through being an ascending and usually bilateral lymphedema. It is highly prevalent in focal areas, hence its alternative title, endemic non-filarial elephantiasis. Podoconiosis (endemic non-filarial elephantiasis) has been recognized as a specific disease entity for over one thousand years and is widespread in tropical Africa, Central America and north India, yet it remains a neglected and under-researched condition (Fig. 1).

HISTORY

From the time of the Roman Empire, travelers recorded anecdotes about people with progressive swelling of the feet. A more detailed reference to 'swollen legs' appears in the Tibetan translations of a fourth century revelation originally recorded in Sanskrit as the second book of rGyud-bzhi (the 'four tantras'). However, it was not until c.905 that the Persian physician Rhazes first distinguished elephantiasis 'of the Greeks' (lepomatous leprosy) from that 'of the Arabs' (most probably non-filarial elephantiasis) (1).

In the 1770s, the adventurer James Bruce gave a graphic description of the elephantiasis he saw in Gondar, northern Ethiopia: "The chief seat of this disease is from the bending of the knee downwards to the ankle; the leg is swelled to a great degree, becoming one size from bottom to top, and gathered into circular wrinkles.... from between these circular divisions a great quantity of lymph constantly oozes. It should seem that the black colour of the skin, the thickness of the leg, its shapeless form and the rough tubercles or excrescences, very like those seen upon the elephant, gave the name to this disease..."

Bruce obtained permission from the emperor, Ras Mikhail, to treat a sufferer, using a range of regimes and medications, but beyond assuaging the patient's thirst with



Fig. 1. Advanced, asymmetrical podoconiosis in a female patient from northern Ethiopia.

a constant supply of whey, no treatment (including hemlock, mercury and tar-water) appeared effective (2).

Through the eighteenth and nineteenth centuries, the pathogenesis of elephantiasis was gradually elucidated through Hendy's study of the lymphatic system in affected people. Wucherer (in Brazil), Lewis (in India), Manson and Bancroft all recognized the role of filarial parasites in elephantiasis, and for a time it was concluded that all elephantiasis was filarial. Towards the end of the nineteenth century, the discrepancy between distribution of elephantiasis and distribution of filaria in North Africa, central America and Europe prompted revision of this theory. Central to current research has been the identification of podoconiosis as a type of elephantiasis distinct from filarial disease. This distinction was first clearly made in 1938, when on the basis of repeated negative tests for bacteria and microfilaria

among Guatemalan patients with elephantiasis, Robles inferred that the disease (which he called 'pseudo-lepra') was associated with walking barefoot (1). He described the ecological niche and the disease process in detail, noting the lifelong nature of the disease, but his enquiry was not continued in South America.

Progress in recognizing the international distribution of non-filarial elephantiasis came as Cohen suggested the use of the term 'idiopathic lymphedema' in place of the local terms 'verrucosis lymphatica' in Kenya and 'mossy foot' in Ethiopia (3). The location of the next set of investigations into non-filarial elephantiasis was western Ethiopia, where in the 1960s, Oomen described a type of elephantiasis caused neither by onchocerciasis nor filariasis (4). He noted that most cases were found between 1000m and 2000m, but was unable to fully resolve questions about etiology.

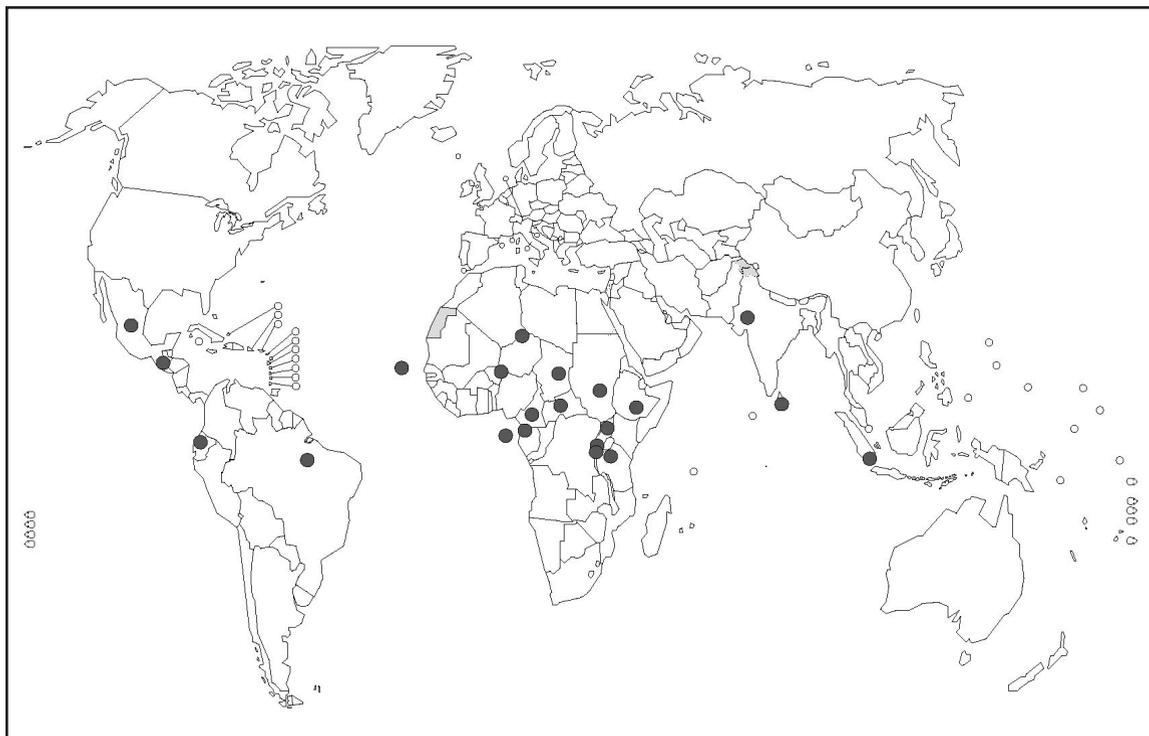


Fig. 2. Global distribution of podoconiosis. (Adapted from WHO website)

Price extended Oomen's epidemiological studies (5,6), and described the etiology (7), pathology (8,9), and natural history (10) of non-filarial elephantiasis in Ethiopia, establishing the term podoconiosis (from the Greek for foot: podos, and dust: konos) (11), which has gained widespread acceptance.

EPIDEMIOLOGY

Geographical Distribution

Podoconiosis is found in highland areas of tropical Africa, Central America and north-west India. Areas of high prevalence have been documented in Uganda (12), Tanzania (13), Kenya (14), Rwanda, Burundi, Sudan and Ethiopia (15), and in Equatorial Guinea (16), Cameroon (17), the islands of Bioko, Sao Tome & Principe (18) and the Cape Verde islands.

The condition has been reported in the

Central American highlands in Mexico and Guatemala south to Ecuador and Brazil in South America (19,20). Further east, on the north coast of South America in Suriname and French Guiana, the distinction between filarial and non-filarial elephantiasis has not been confirmed. Although filarial elephantiasis predominates in India, podoconiosis has been reported from north-west India, Sri Lanka and Indonesia (Fig. 2).

Price holds that podoconiosis was previously common in North Africa (Algeria, Tunisia, Morocco and the Canary Islands) and Europe (France, Ireland and Scotland) but is no longer found in these areas since use of footwear has become standard (19).

Prevalence

Prevalence estimates have been made in Ethiopia and, recently, in Cameroon. Early estimations of prevalence using counts of

attendees at fifty-six markets ranged from 0.42 to 3.73% (4), and further investigation in Wollamo zone, southern Ethiopia demonstrated prevalence of 5.38% across five markets. In the village of Ocholo, located at 2000m altitude in the mountains west of Lake Abaya, southern Ethiopia, elephantiasis was present in 5.1% of long-term residents (21), while in two resettlement schemes in Ilubabor, western Ethiopia, 9.1% of long-term residents were affected, and 5.2% of people resettled some 7-8 years previously (22). More recent population-based surveys in northwest (23), southern (24) and western Ethiopia (personal communication), and northwestern Cameroon (17), have documented prevalence of 6%, 5.4%, 2.8% and 8.1%, respectively.

Age, Gender and Occupation

Early reports based on clinic attendees cannot be relied upon to derive an accurate sex ratio. Price found a male: female ratio of 1:1.4 in market studies, which he attributed to greater use of footwear by men (7). Genene Mengistu documented a male: female ratio of 1:4.2 in a survey in Ocholo, but many men of working age were absent from the community at the time (21). By contrast, Kloos noted higher prevalence among men in three of four resettlement communities in Keffa Region (22). In a single village in Pawe, Hailu Birrie found a male: female ratio of 1:1.4 among sufferers (23). The most recent community-based study recorded a gender ratio among podoconiosis sufferers (1:0.98) that was not significantly different from the zonal gender ratio (1:1.02) (24).

All of the major community-based studies have shown onset in the first or second decade and a progressive increase in podoconiosis prevalence up to the sixth decade. Development of podoconiosis is closely associated with living and working barefoot on irritant soils. Farmers are at high risk, but the risk extends to any occupation with prolonged contact with the soil, and the condition has been noted among potters,

goldmine workers, and weavers who sit at a ground level loom.

Geology and Climate

An association between podoconiosis and exposure to the local soil was suspected by Robles in Guatemala at the end of the nineteenth century. However, it was not until Price superimposed maps of disease occurrence onto geological surveys that persuasive evidence of a link with red clays derived from volcanic activity was provided (15,25). The climatic factors necessary for producing irritant clays appear to be high altitude (between 1000 and 2500m above sea level) and seasonal rainfall (over 1000mm annually). These conditions contribute to the steady disintegration of volcanic ash and the reconstitution of the mineral components into silicate clays. Comparison of soil from an endemic area with that from outside the area revealed high levels of beryllium and zirconium (both known to induce granulomata) (26), but the role of these elements is not yet established.

Although the earlier literature on podoconiosis suggested quartz to be a causal agent, it is possible that kaolinite/smectite or smectite clay particles are etiologically involved. Military surgeons in the United States of America first recognized the biologically active properties of sterile soil in the 1970s. Early research identified clay particles (<2µm diameter) as more powerful than sand (2µm<x<20µm) or silt (20µm <x<2mm) in potentiating the effect of infection in wounds. Of the smectite (stacked) clays studied, montmorillonite was found to be a more powerful potentiator than kaolinite or illite (27). In the last decade, research into the health effects of silicate particles has shifted to focus on the role of ultrafine (nano-) particles (28). A range of experiments have demonstrated toxic effects of ultrafine particles, including neutrophil influx, increases in markers of oxidative stress, and adverse effects on macrophage phagocytosis

(29). Particle size has been shown to be more important than surface reactivity in causing cytotoxicity through apoptosis and necrosis (30). Ongoing studies comparing soils from endemic and non-endemic areas aim to characterize the mineral trigger.

Pathology and Pathogenesis

The pathogenesis of podoconiosis is not yet fully elucidated. At present, most evidence suggests an important role for mineral particles on a background of genetic susceptibility, but the possible role of other co-factors (for example chronic infection or micronutrient deficiencies) has not been explored. Colloid-sized particles of elements common in irritant clays (aluminum, silicon, magnesium and iron) have been demonstrated in the lower limb lymph node macrophages of both patients and non-patients living barefoot on the clays (9). Electron microscopy shows local macrophage phagosomes to contain particles of stacked kaolinite ($\text{Al}_2\text{Si}_2\text{O}_5(\text{OH})_4$).

Price describes changes in the dermis, afferent lymphatics and lymph nodes of affected individuals. The primary lymphatics become dilated and surrounded by lymphocytes, while edema and disorganized collagen production occurs. This fibrosis affects the afferent lymphatics, narrowing and eventually obliterating their lumen. If fibrosis predominates, both dermis and subdermis become bound to underlying deep fascia by collagen fibers, eventually destroying sweat and sebaceous glands and hair follicles. If edema predominates, afferent vessel walls become rigid and dilated, provoking valvular dysfunction (8). No animal model has yet been developed for podoconiosis, but experiments have shown that silica suspension injected into rabbit lymphatics can provoke intense macrophage proliferation followed by lymphatic fibrosis and blockage (31). Further histopathology and imaging studies using modern methods will be vitally important to understanding pathogenesis but are limited

by the remote locations of most podoconiosis communities.

Clinical Pathology

The pathology and natural history are described in a range of articles (3,10,32). Podoconiosis is characterized by a prodromal phase before elephantiasis sets in. Early symptoms commonly include itching of the skin of the forefoot and a burning sensation in the foot and lower leg. Early changes that may be observed are splaying of the forefoot, plantar edema with lymph ooze, increased skin markings, hyperkeratosis with the formation of moss-like papillomata, and 'block' (rigid) toes. The 'mossy' changes predominate in a slipper pattern around the heel and border of the foot, reflecting the distribution of underlying superficial lymphatics (*Fig. 3*).

Later, the swelling may be soft and fluid ('water-bag' type); or hard and fibrotic ('leathery' type), often associated with multiple hard skin nodules (19), or intermediate with both sets of features. Acute episodes (acute adenolymphangitis, ALA) occur on average 5 times per year, and patients become pyrexial with a warm, painful limb, necessitating on average 4.5 days off work each episode (personal communication). These episodes appear to be related to progression to the hard, fibrotic leg.

Genetics

Among many families, exposure to irritant soil is more or less uniform, yet not all family members will develop podoconiosis during their lifetime. Recent studies in a southern Ethiopian population demonstrate the contribution of both genetic and environmental factors to the pathogenesis of podoconiosis. The estimated heritability was 63%, with sibling recurrence risk estimated as 5.1. The 'best-fitting' genetic model was an autosomal co-dominant major gene with age and footwear as significant covariates (33).



Fig. 3. 'Slipper' pattern mossy changes.

A genome-wide association study has shown significant association between podoconiosis and single nucleotide polymorphisms (SNPs) in or near the *HLA-DQB1*, *HLA-DQA1* and *HLA-DRB1* genes (personal communication).

ECONOMIC AND SOCIAL CONSEQUENCES

Economic Consequences

A comparative cross-sectional study was performed in 2005 to calculate the economic burden in a zone endemic for podoconiosis. Total productivity loss for a patient amounted to 45% of total working days per year, and in a zone of 1.5 million people, the total overall annual cost of podoconiosis was calculated to exceed US\$ 16 million per year (34). Projected to the whole of Ethiopia, the direct and productivity costs would amount to at least US\$ 208 million per year.

Social Stigma and Access to Health Care

Social stigma against people with podoconiosis is rife, patients being excluded from school, denied participation in local

meetings, churches and mosques, and barred from marriage with unaffected individuals (35). Price reports one podoconiosis sufferer as having remarked that 'it would be better to have leprosy,' since stigma surrounding leprosy has diminished as a consequence of effective medicine and health care services (6). The belief that there is no effective medical treatment may act as a barrier to accessing health care.

Understanding of and attitudes towards podoconiosis in local communities has been investigated in Ethiopia and Cameroon. In Cameroon, most (77.8%) respondents knew a descriptive local term for the condition, and 81.4% recognized the disease when prompted with a photograph (17). These findings are consistent with those in a community endemic for podoconiosis in southern Ethiopia (36). Almost all (91.6%) adult respondents in this study knew local terms for podoconiosis, and 93.5% recognized the disease when shown a photograph.

Both studies demonstrated stigmatizing attitudes towards disease in endemic communities – in Cameroon only 7.2% thought that healthy community members

would consider marrying a person with lymphedema (17), in Ethiopia 53.9% would not eat with a person with podoconiosis (36). Such attitudes may be linked to relatively low levels of awareness of treatment: only 32% of the Cameroonians interviewed and 41.4% of Ethiopians were aware that treatment was available. More worryingly, more than half of the Ethiopian health professionals interviewed thought podoconiosis was an infectious disease, and all held at least one stigmatizing attitude towards podoconiosis patients (37).

The potential harm that may be done to patients through research that identifies them as having podoconiosis is very real for such a thoroughly stigmatizing disease. Strategies to minimize the consequences of research on podoconiosis stigma have been investigated and may be used by other groups planning research in podoconiosis (38).

CLINICAL ASPECTS

Assessment of Disease: Staging System

Investigators in Ethiopia developed a staging system with the aims of enabling disease burden to be measured and interventions to be assessed (39). Initial attempts to validate the Dreyer system (a seven-step system for staging filarial elephantiasis) (40) indicated that this existing system did not transfer adequately to podoconiosis. A new system was developed through a series of iterative field tests. This system is designed to be used by community workers with little health training, has five stages, and is based on the proximal spread of swelling, knobs and bumps. The stage is recorded together with presence or absence of mossy changes (M+ or M-) and the greatest below-knee circumference. The repeatability and validity of the staging system were assessed and showed good inter-observer agreement and repeatability. The staging system has, anecdotally, been adopted with enthusiasm by patients who are grateful for

a method by which their treatment efforts can be measured.

Assessment of Disease: Cardiff Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) was developed to measure quality of life by investigators in Cardiff in 1994 (41). Investigators in Ethiopia had the DLQI translated and back translated twice according to the authors' instructions, and assessed feasibility of use, internal consistency and concurrent validity among podoconiosis patients in southern Ethiopia (42). The DLQI was easy to administer, taking approximately 4 minutes per patient. The overall value of Cronbach's alpha was 0.90, indicating high internal reliability. Concurrent validity was assessed through comparison of patients at first visit to the treatment outreach clinic with those who had been treated for at least three months (median scores 13 and 3, respectively, $p < 0.001$). The investigators concluded that the Amharic DLQI was another useful tool in assessing podoconiosis patients at presentation, and in evaluating physical and social interventions.

Differential Diagnosis

The conditions podoconiosis must most often be distinguished from are filarial and leprotic lymphedema, endemic Kaposi's sarcoma and chronic recurrent erysipelas. Clinical features of podoconiosis that help distinguish it from filarial elephantiasis include the foot being the site of first symptoms (rather than elsewhere in the leg) and bilateral but asymmetric swelling usually confined to the lower leg (compared to the predominantly unilateral swelling extending above the knee in filariasis). Groin involvement in podoconiosis is extremely rare. A recent study using both midnight thick film examination and BinaxTM antigen cards has confirmed that in a podoconiosis-endemic

area, community workers' diagnoses are highly predictive of podoconiosis (43). Podoconiosis may be distinguished from leprosy lymphedema by the preservation of sensation in the toes and forefoot, the lack of trophic ulcers, thickened nerves or hand involvement.

PREVENTION AND TREATMENT

Primary Prevention

Evidence suggests that primary prevention should consist of avoidance of prolonged contact between the skin and irritant soils. This may be achieved by use of robust footwear or covering of floor surfaces in areas of irritant soil. An Ethiopian national non-government organization, the Mossy Foot Prevention and Treatment Association (MFTPA), trains treated patients to make low-cost durable leather boots and shoes for their communities in an attempt at primary prevention. In addition, new partnership with TOMS Shoes (a US-based business whose founding principle is to give away a pair of shoes to a child in need for every pair sold) has allowed the distribution of nearly 100,000 pairs of shoes through podoconiosis prevention programs in Ethiopia since 2009. Operational research to measure the effect of this prevention campaign is much needed.

Secondary Prevention

Secondary prevention (prevention of the progression of early symptoms and signs to overt elephantiasis) takes the form of training in foot hygiene (washing daily with soap and water, using antiseptics and ointment), and use of socks and shoes. Compression bandaging is highly effective in reducing the size of the soft type of swelling, but bandages are often difficult for patients to afford. Progression can be completely averted if these measures are strictly adhered to, but compliance must be life-long (44). Relocation from an area of irritant soil (10) or adoption of a

non-agricultural occupation are also effective but may not be feasible for the patient.

Tertiary Prevention

Tertiary prevention (the management of those with advanced elephantiasis) encompasses secondary prevention measures, elevation and compression of the affected leg, and, in selected cases, removal of prominent nodules. For elevation to be successful, at least 18 hours with the legs at or above the level of the heart are needed each day. Previously, Charles' operation (removal of skin, subcutaneous tissue, and deep fascia to lay the muscles and tendons bare, followed by grafting of healthy skin), or a variant, was used (3,19), but long-term results are disappointing. Follow-up of patients suggests that those unable to scrupulously avoid contact with soil experience recurrent swelling which is more painful than the original disease because of scarring. Social rehabilitation is vital and includes training treated patients in skills that enable them to generate income without contact with irritant soil. Successful training in shoemaking, bicycle repair, hairdressing and beauty care, electronics and carpentry has been given to several hundred treated patients by the MFTPA in southern Ethiopia.

International Health Aspects

Worldwide, very few public or private sector organizations offer treatment to people with podoconiosis. This is the result of a lack of evidence-based treatment options compounded by patchy acknowledgment that the disease even exists. In southern Ethiopia, a local non-government organization, the Mossy Foot Treatment & Prevention Association (MFTPA), has pioneered prevention and treatment using a low-tech community-based intervention. The program was recently evaluated (45) against a model devised for control of chronic diseases in low-income settings, the WHO Innovative Care

for Chronic Disease Framework, ICC (46). The evaluation describes the structure and aims of the program and identifies areas of the program that require strengthening.

Podoconiosis currently lacks an international advocacy body and, therefore, lacks profile and voice at international level. The WHO Department for Control of Neglected Tropical Diseases has indicated willingness to include podoconiosis in its remit by the close of 2010.

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