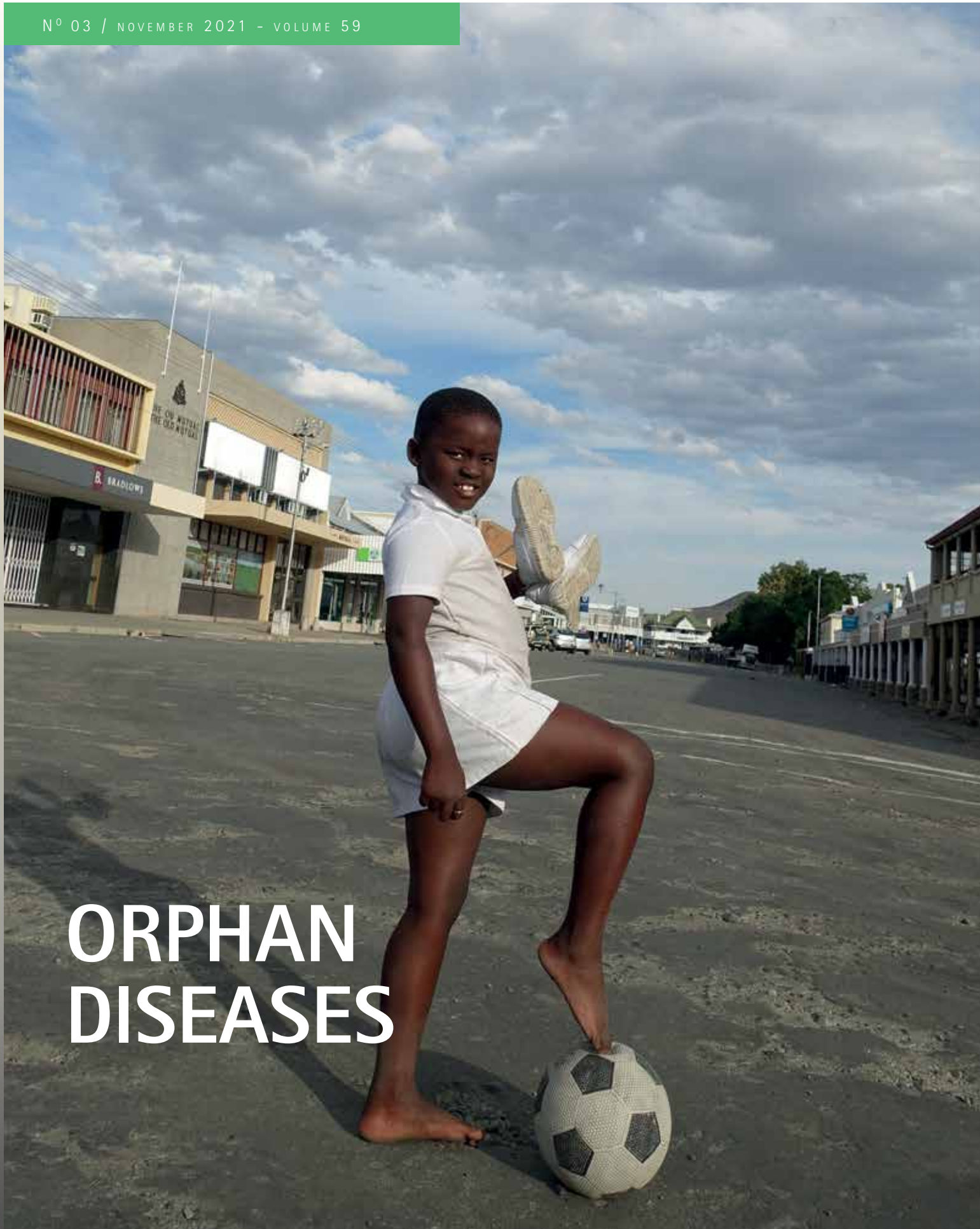
MTb

BULLETIN of the NETHERLANDS SOCIETY for TROPICAL MEDICINE and INTERNATIONAL HEALTH

Nº 03 / NOVEMBER 2021 - VOLUME 59



ORPHAN DISEASES

CONTENT

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In the year 2000, the 'big three' dominated tropical medicine: malaria, HIV/AIDS and tuberculosis. Virtually all research efforts went to those three conditions that no doubt affected millions of people all over the world. While the highest burden was and is in Africa, HIV/Aids is rapidly spreading to high-income countries (HICs) leading to an unprecedented effort in research aimed at identification of the virus, development of a diagnostic test and, eventually, effective treatment, with major public health campaigns focusing on prevention and awareness.

As a result, little attention and funding was available for the so-called neglected tropical diseases (NTDs). Médecins Sans Frontières (MSF), who primarily work in the field, were the champions to promote these classical tropical conditions (leprosy, schistosomiasis, and leishmaniasis, among others), as the neglect affected patient management, in particular the lack of effective drugs. Later the non-communicable diseases (NCDs) were also given the attention they deserved; both NTDs and NCDs affect millions of people.

While most patients in low- and middle-income countries would fall in one or more of the above categories of diseases, a small group of forgotten diseases remains. These are often found among poor populations who live in remote areas and who have no voice. As these conditions generally occur in small numbers of people, this makes it difficult to compete with other more common (tropical) diseases, especially those that affect people from HICs including tourists.

This issue of MT*b* aims to draw attention to these forgotten, rare diseases.

Klaas Marck's encounter with noma was coincidental, but he made it his life work, resulting in numerous missions and publications. It is not a coincidence that he features in the first new rubric in which we aim to interview anyone (both 'young' and 'old') who has a story to tell in global health and tropical medicine.

We present a spectrum of rare diseases, aimed at informing the readership of their existence, but also at guiding those in training for work in the tropics. Some are easy to diagnose, while others require more advanced tools or are diagnosed clinically. Some are restricted to the tropics; others occur in travellers or migrants. In the extended case report, the emphasis is on the differential diagnosis of a particular and common presentation in a certain epidemiological setting – a common clinical problem. But it is not all about clinical management; Esther Jurgens puts these rare diseases in perspective and addresses ethical issues in the neglect.

It is our aim to increase awareness of the existence of these rare and orphan diseases and provide some guidance for medical doctors in global health and tropical medicine (in training) who may come across these conditions in their work. We also wish to draw attention to the underlying ethical and moral implications when it comes to dealing with these 'orphan patients': the patients suffering from disease many of us may not know about, but that still affect large numbers of people worldwide.

Ed Zijlstra, Maud Ariaans

Global health dilemmas: when rare diseases become orphan diseases

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THE CONTEXT

The number of diagnosed rare diseases varies between 5,000 and 8,000, affecting around 400 million people worldwide and resulting in some 5% of the population living with a rare disease – the vast majority of them in low- and middle-income countries (LMICs).[1] Though new rare diseases continue to be discovered, exact numbers are difficult to determine because they are often misdiagnosed as something else.[2] A disease is called 'rare' when the condition affects fewer than 200,000 people, and the majority have genetic origins (80%).[1] Every second 'rare patient' is a child, and three out of ten young patients do not reach their 5th birthday.[2] As the disease is rare, medical and scientific knowledge of these conditions is also rare. Those that do get more (scientific) attention are the ones that are more well-known in high-income countries (HICs), such as Lou Gehrig's Disease (ALS) and cystic fibrosis.[2] Many of the rare diseases can't be cured, though appropriate treatment and medical care can vastly improve the quality of life. In addition, besides medical consequences, often patients suffering from these diseases are socially, economically and culturally vulnerable, and find themselves in isolation; or worse, they are subjected to human rights violations such as mental and physical violence, discrimination and abuse.[3]

WHEN RARE DISEASES BECOME 'ORPHANS'

A rare disease may become an orphan disease because of two reasons: when a disease affects less than 200,000 people, and by default, when there are not enough patients to make research and drug development cost-effective.[4]

As with other poverty related diseases, rare diseases are often neglected or ignored. While progress in rare disease treatment in the West has grown, this is not the case for Africa – the continent which remains most vulnerable to rare diseases and where treatment and research for these conditions is not a key priority.[5] Also resources may be limited because of a high prevalence of communicable diseases such as malaria, HIV/AIDS and tuberculosis. Only when a rare disease comes close(r) to home – as with the Ebola outbreaks (2013-2016) in West Africa spreading to HICs – is the international response to the epidemic, including vaccine development, accelerated. In summary, as the word orphan implies, both rare and tropical diseases are considered 'orphans' in terms of low public attention and lack of research and funding for treatment and care.

ETHICAL DILEMMAS

Both rare and orphan diseases present considerable challenges and ethical dilemmas. From an utilitarian ('greatest good for the greatest number of people') and a cost-effectiveness approach, these diseases are on the losing end of the spectrum, in particular when it comes to the allocation of funds for developing treatment strategies and orphan drugs. According to Kontoghiorghe et al. (2014), this is a major global health challenge and conflicts with a rights-based approach to health. The term orphan drugs was introduced by governments in LMICs to help in the production and marketing of medicinal drugs by the pharmaceutical industry for patients suffering from rare conditions.[6] The ethical connotation of the concept is related to the need to ensure patients suffering from these conditions the same quality of treatment as other patients with more common diseases.[6]

OF RAISING AWARENESS AND BROADENING SCOPE

In his statement on the occasion of the 2018 celebration of the Rare Disease Day,[7] World Health Organization Director-General Tedros Ghebreyesus underlined the universal health coverage (UHC) and sustainable development goal (SDG) principles of equitable access to diagnosis and care for rare patients. In particular, he referred to accessing sustainable medicines. Universal health coverage can't be reached without caring for patients with a rare disease: "Just because a disease affects a small number of people does not make it irrelevant or less important than diseases that affect millions."[8]

The International Rare Diseases Research Consortium (IRDiRC) is one of the organisations taking up the challenge of ensuring that patients living with a rare disease receive accurate diagnosis, care and treatment. It has been instrumental in promoting research and advocating for more scientific as well as political and economic attention for these conditions. Given the particularities of rare diseases, international collaboration and sharing of knowledge is of utmost importance, as well as broadening the focus from countries in the Western World to the regions where the diseases are very prevalent, yet understudied and underserved. This edition of MT*b* is a good example of how this can be done.

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3. A rare, non-contagious, genetically inherited condition, with high prevalence in SSA (estimates of 1 in 1,400 people being affected in Tanzania, and as high as 1 in 1,000 reported for select populations in Zimbabwe and for other specific ethnic groups in Southern Africa). The condition is often misunderstood, with myths and superstition leading to discrimination, social exclusion and in some communities seriously putting the security and lives of persons with albinism at risk, see: www.un.org/en/observances/albinism-day and Horlings' article on skin cancer in the tropics elsewhere in this edition of MT*b*.
4. Definition of an orphan disease: "A disease that has not been adopted by the pharmaceutical industry because it provides little financial incentive for the private sector to make and market new medications to treat or prevent it. An orphan disease may be a rare disease (according to US criteria, a disease that affects fewer than 200,000 people) or a common disease that has been ignored (such as tuberculosis, cholera, typhoid, and malaria) because it is far more prevalent in developing countries than in the developed world." MedicineNet [Internet]. San Clemente: MedicineNet, Inc.; c1996-2021. Medical definition of orphan disease; reviewed 2021 Mar 29. Available from: www.medicinenet.com/orphan_disease/definition.htm
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Case history: a 24-year-old farmer from Northwest Ethiopia with swollen legs and nodules on the feet

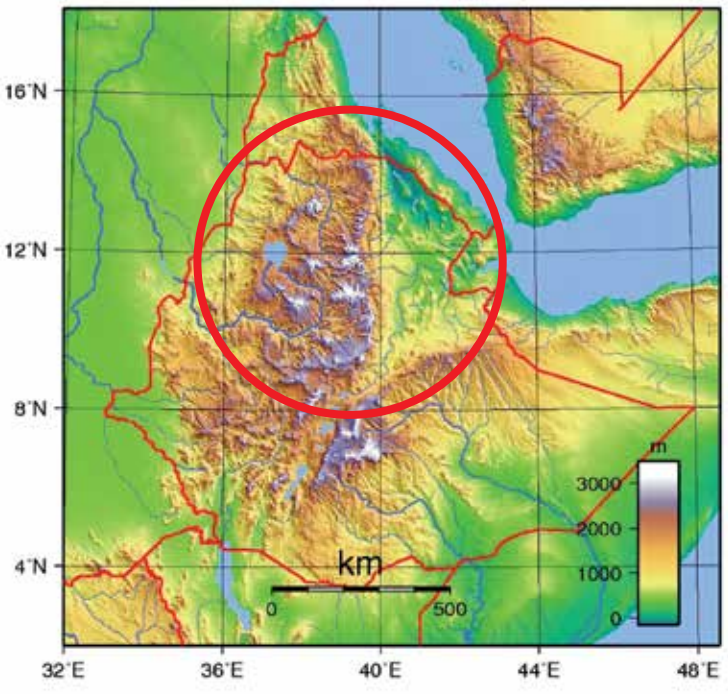

Figure 1. Map of Ethiopia with Amhara Region indicated, 500 to 4,620 meter above sea level.

HISTORY

A 24-year-old farmer presents to your clinic in the Amhara Region of Northwest Ethiopia (Figure 1). He complains of progressive swelling of the feet over the last eight years with a burning sensation, and development of firm nodules particularly on the toes, that were increasingly itchy.

Further history and previous medical history are unremarkable. He has lived his whole life in the area and did not travel.

SETTING

Your clinic is in a remote area at a height of 2,600 meter, with an outpatient department, two general wards with twenty beds, and a maternity ward. It has a basic laboratory where basic haematology, urine, malaria tests, stool for parasites, sputum for acid-fast bacilli (AFBs) and an HIV test can be done; there is an X-ray machine and ultrasound scans can be performed. Medication for the most prevalent diseases is available, as well as vaccines for the EPI programme. Supplies come usually every two weeks from the nearest regional hospital, one day's driving away. Blood and other material for specific tests can be sent to the regional laboratory.

CLINICAL FINDINGS

Figure 2. Bilateral swelling of the legs and multiple firm nodules of different sizes mainly on the toes.

On examination, he is well with normal vital signs. No abnormalities are found on examining head and neck, chest, and abdomen. The only abnormalities are found on the legs; there was non-pitting oedema, and the skin feels rough on palpation. There are multiple medium to large sized nodules that are fixed to the skin and firm on palpation. There are multiple bilateral palpable lymph nodes in the legs and in the inguinal area.

LABORATORY RESULTS

Normal haematological parameters. HIV test: non-reactive.

QUESTION 1

a. Consider the following differential diagnoses, and give the main characteristics of each of the differential diagnoses listed:

- filarial lymphoedema
- Kaposi's sarcoma ('classic type')
- leprosy
- podoconiosis
- mycetoma (Madura foot)
- Milroy's disease
- longstanding oedema due to cardiovascular disease
- myxoedema
- chromoblastomycosis

b. What is the most likely diagnosis given the clinical picture and geographical epidemiology?

QUESTION 2

What additional investigations would you like to do to establish the likely diagnosis? (Remember you are working in a resource-restricted setting).

QUESTION 3

How would you manage the patient?

For answers, see page 6 and 7

ANSWERS TO QUESTION 1

(a. Give the main characteristics of each differential diagnosis.)

(b. What is then the likely diagnosis given the clinical picture and geographical epidemiology?)

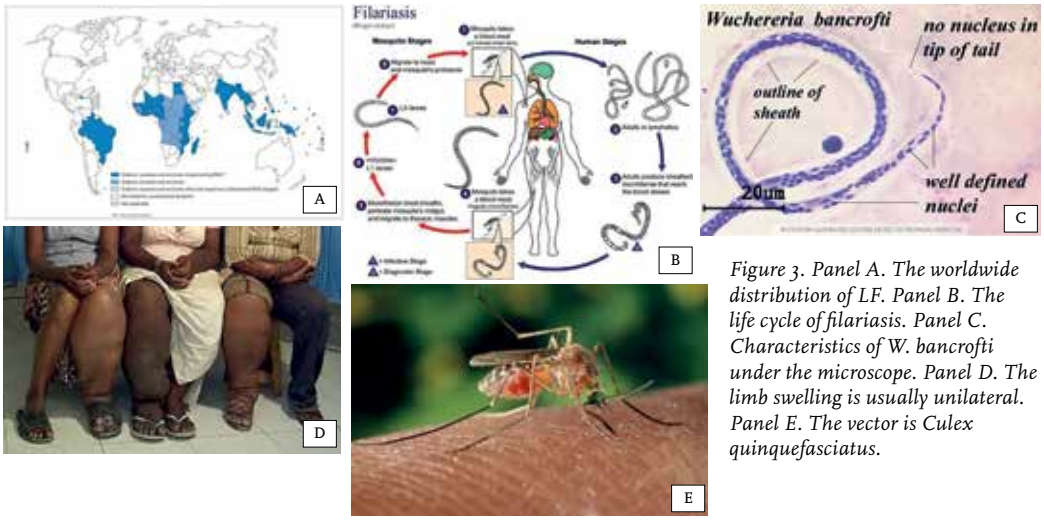

Figure 3. Panel A. The worldwide distribution of LF. Panel B. The life cycle of filariasis. Panel C. Characteristics of W. bancrofti under the microscope. Panel D. The limb swelling is usually unilateral. Panel E. The vector is Culex quinquefasciatus.

FILARIAL LYMPHOEDEMA (FIGURE 3 A-E)

There are three important manifestations of filarial disease: onchocerciasis, lymphatic filariasis (LF) and loiasis. This region is endemic for LF only. In LF, the microfilaria is transmitted by a Culex mosquito. *Wuchereria bancrofti* is the most important filarial species. The adult worms lodge in the lymphatics usually in the inguinal area causing obstruction of lymphatic flow leading to chronic lymphoedema. Subsequent severe swelling causes cracks in the skin and secondary bacterial infection that aggravate the swelling, discomfort, and disability. Similar giant swelling may occur in the scrotum. Treatment is with antiparasitic drugs and skin hygiene to reduce infection.

KAPOSI'S SARCOMA (HIV RELATED, OR THE 'CLASSIC TYPE') (FIGURE 4 A, B)

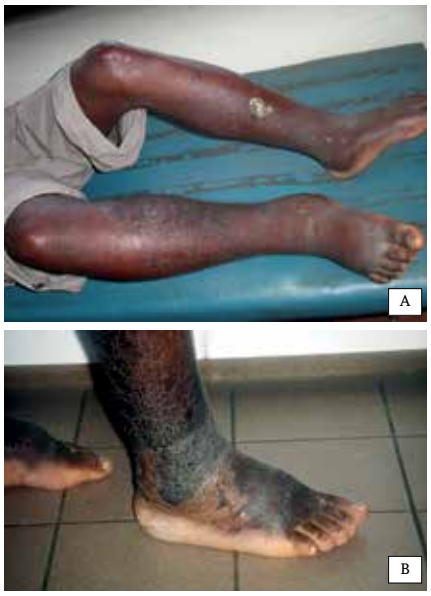

Figure 4 A. Kaposi's sarcoma in an HIV positive patient. B. Classical Kaposi's sarcoma.

Kaposi's sarcoma (KS) is very common across Africa in the context of HIV infection. It is a World Health Organization Clinical stage 4 condition and occurs in patients with very low CD4 counts <200 cells/mm^3. It is caused by human herpesvirus (HHV) 8. In addition to a positive HIV test, one would look for KS in other sites such as the buccal mucosa, and other parts of the skin. Treatment is with chemotherapy and antiretroviral therapy.

In addition, KS may present as the classical type that affects elderly men and that runs an indolent course. Here, the patient is HIV negative. The classic type is usually present in middle aged and older men. It is uncommon in Ethiopia.

LEPROSY (FIGURE 5 A-C)

Leprosy is caused by *Mycobacterium leprae* and leads to a spectrum of clinical manifestations. Transmission is principally from mother-to-child during nursing. The bacilli can be demonstrated by microscopy in scrapings or by PCR. On one end of the spectrum, where the immune response is strong, is tuberculoid leprosy – these patients have a relatively low bacillary load (paucibacillary leprosy) with severe destruction of tissues; on the other end of the spectrum is lepromatous leprosy with a weak immune response – these patients harbour high numbers of bacilli (multibacillary leprosy); there is local spread but little necrosis. Sensory loss is an important feature (absent in this patient). Treatment is with anti-leprosy drugs. Leprosy control efforts have been successful due to concerted efforts over the last six decades; in Ethiopia, new leprosy cases have now dropped from 80,000 in 1985 to 3,000 in 2016. With waning interest by national control

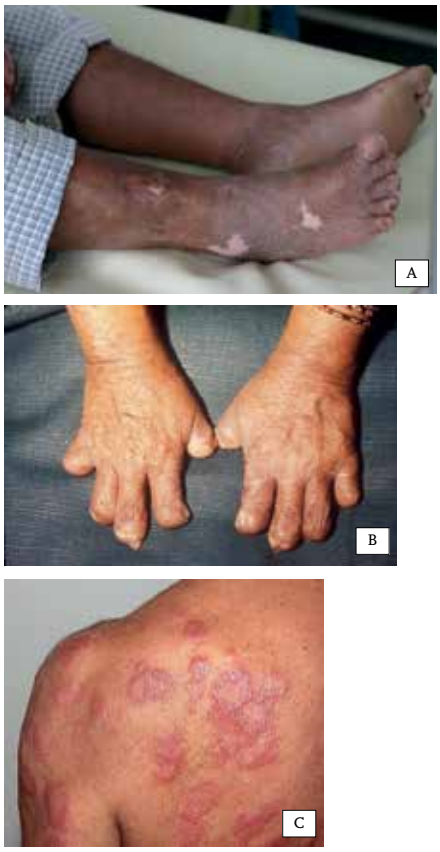

Figure 5. Panel A. Leprosy on the foot with scars of previous surgery. Panel B. Typical loss of digits in tuberculoid leprosy. Panel C. Typical skin lesions in tuberculoid leprosy. (Courtesy Dr JB Visser)

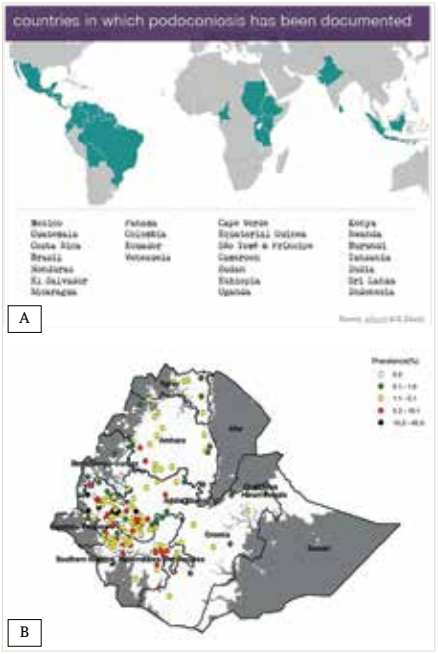

Figure 6. Panel A. Worldwide distribution of podoconiosis. Panel B. Distribution of podoconiosis in Ethiopia. (Courtesy Dr JB Visser)

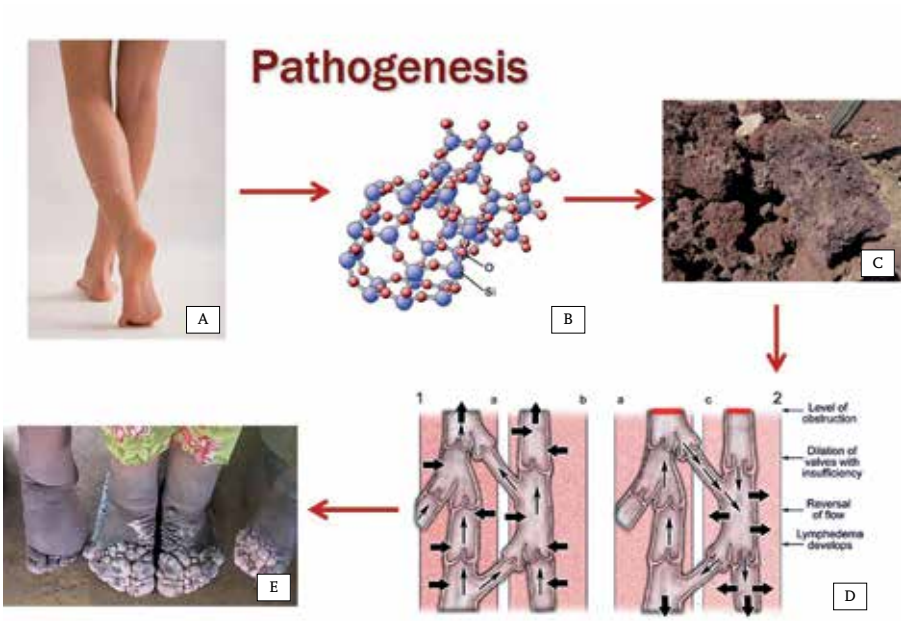

Figure 7. Pathogenesis of podoconiosis. Panel A. Walking on bare feet is a risk factor. Panel B, C. Silica particles present in the soil enter the skin. Panel D. Obstruction of lymphatics leads to lymphoedema. Panel E. Severe clinical disease. (Courtesy Dr JB Visser)

programmes, transmission is ongoing, and new cases continue to appear.

PODOCONIOSIS (FIGURE 6,7)

The name is derived from the Greek *podos* (foot) and *konos* (dust). It is also known as tropical elephantiasis, endemic non-filarial elephantiasis, mossy foot disease, microcrystal disease, big foot disease or lymphostatic verrucosis. It is distinct from LF; it is a non-communicable disease. It has a worldwide distribution and is common in Ethiopia. An estimated 1 million people are affected in Ethiopia, and 0.5 million in Cameroon.

Clinically it is characterised by ascending, commonly bilateral but asymmetric, lymphoedema. It is caused by exposure to irritant soils, usually red clay soil near volcanoes. Tiny micro particles of silica from the volcanic soil and aluminosilicates penetrate the skin. There is 5-10% prevalence in areas of irritant soil and subsistence farming.

In the prodromal phase, there may be itching, burning, splaying of forefeet and 'block toes' occur, followed by plantar oedema and hyperkeratosis. This is followed by soft 'water bag' type swelling or hard fibrotic, 'leathery' type swelling, associated with multiple skin nodules.

This is the most likely diagnosis, because of the geography and history of the patient who walks and works on bare feet. He presents with an ascending clinical course in the leg, starting in the feet, progressing to the knee, and rarely affecting upper leg or groin. It is bilateral yet asymmetric. Podoconiosis occurs at an altitude of ≥1,500 meter (where there is no filarial transmission). However, filarial lymphoedema needs to be excluded anyway in this context as the treatment would require anti-filarial drugs.

ANSWER TO QUESTION 2

(What additional investigations would you like to do to establish the likely diagnosis?)

In vitro immunodiagnostic assay for the detection of *W. bancrofti* antigen; this comes back as 'negative'. Together with the clinical picture and the fact he had stayed life-long in the area, podoconiosis is the most likely diagnosis.

ANSWER TO QUESTION 3

(How would you manage the patient?)

The main issues are:

TREATMENT (FIGURE 8)

- There is no specific treatment. Foot hygiene with soap, antiseptics ointment, pressure bandages, and wearing socks and shoes are effective in reducing the stage of disease, with reduction of leg circumference and improved quality of life (Figure 6)
- Occasionally nodulectomy is indicated
- Social rehabilitation

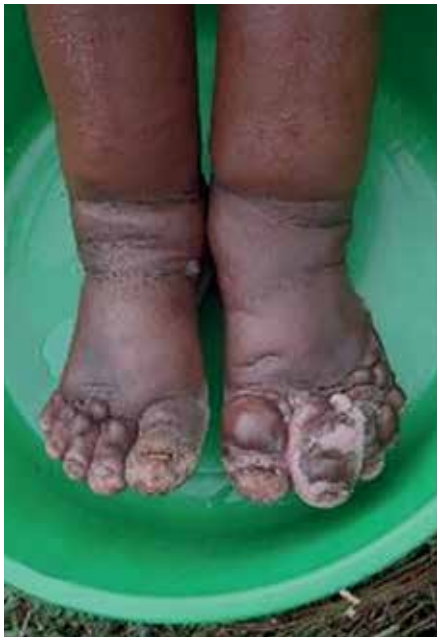

Figure 8. Regular footbaths improve foot hygiene and lead to reduction of the swelling and disability. (reproduced with permission from Sikorski, et al, PLoS NTD 2010;4(11):e902)

PREVENTION

- Awareness in endemic areas; there are few dedicated disease control programmes worldwide
- Community education, reducing stigma
- Providing shoes free of charge

ELIMINATE BECAUSE OF THE FOLLOWING

- Entirely preventable disease 'Prevent Podoconiosis, Wear Shoes';
- Large window of opportunity (10 years of persistent contact before symptoms start to appear)
- Non-communicable disease (no human carrier, no flying vector or animal reservoir);
- Easy detection (clinically distinguishable from LF)
- Exists only in localized regions with specific climatic criteria
- Management synergy with other NTDs

HOW IS THE ETHIOPIAN FARMER DOING?

He has almost fully recovered after intensive secondary prevention, and has found a new job as an orthopaedic shoemaker providing tailor-made shoes for patients with podoconiosis (Figure 9).

Figure 9

DISCUSSION OF THE OTHER DIFFERENTIAL DIAGNOSES

MYCETOMA (MADURA FOOT) (FIGURE 10)

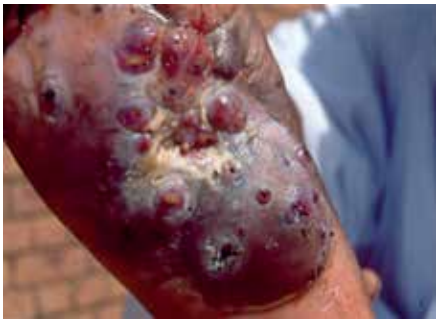

Figure 10. Mycetoma of the foot. The clinical triad is swelling, sinus formation and discharge of grains.

Mycetoma may be caused by bacteria (actinomycetoma) or fungi (eumycetoma). It has a worldwide distribution with actinomycetoma being most common in Mexico and eumycetoma in Sudan. This is an infection by implantation; the organism enters through the skin usually on the foot in people who do not wear shoes. There is a clinical triad: swelling, sinuses, and expulsion of grains. The disease leads to severe morbidity and stigma; it affects mainly young adults. Treatment is with antibiotics or antifungals.

MILROY'S DISEASE

This is a very rare hereditary condition that is characterised by congenital abnormalities of the lymphatic system, usually leading to unilateral lower extremity lymphoedema.

LONGSTANDING OEDEMA DUE TO CARDIOVASCULAR DISEASE

This is a form of bilateral ankle oedema ascending to the lower and upper leg in severe cases. It is typically pitting oedema, but in longstanding cases the oedema may become indurated. Clinically one looks for symptoms and signs of heart failure; underlying heart disease may be post-myocarditis, alcoholic cardiomyopathy, hypertensive cardiomyopathy, or rheumatic heart disease. Ischemic heart disease is uncommon in most parts of Africa.

MYXOEDEMA IN THYROID DISEASE (FIGURE 11)

This is a feature in auto-immune thyroid disease. Clinically, patients may have

hyper- or hypothyroidism; in others the thyroid function may be normal.

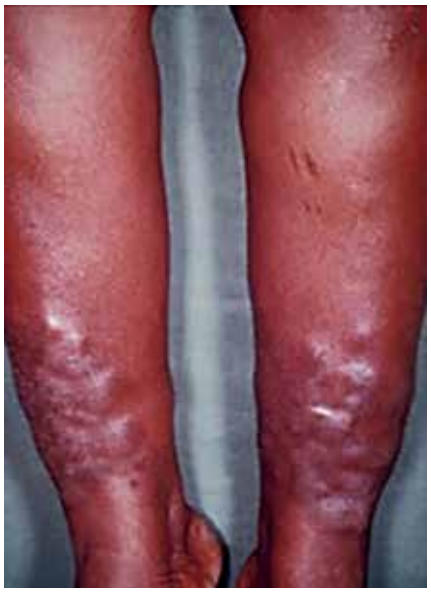

Figure 11. Myxoedema (source Wikipedia).

CHROMOBLASTOMYCOSIS (FIGURE 12)

Chromoblastomycosis is a chronic fungal infection of the skin and subcutaneous tissue, most commonly of hands, feet and lower legs. It is typically caused by traumatic percutaneous inoculation of the fungal genera *Fonsecea, Phialophora* and *Cladophialophora*, which are found in plant debris or tropical detritus. Infection ocurs worldwide but is most common in rural (sub)tropical areas. Male agricultural workers are most commonly affected.

Painless lesions develop slowly over years from the site of inoculation as verruccous nodules or plaques, gradually spreading centripetally by lymphatic or cutaneous dissemination. Typical complications are ulcerations, chronic lymphoedema, and even elephantiasis and bacterial superinfection.

Diagnosis is made by direct microscopic detection of pathognomonic sclerotic cells in skin scrapings on a simple wet film; hyphae are seen on a potassium hydroxide preparation. More sophisticated techniques (e.g. culture, serology, PCR) are rarely available in endemic areas. Infection is not life-threatening (unless in immune-supressed patients), but is difficult to treat (long-standing therapy, usually combination of anti-fungals).

Here, history and clinical picture of the patient could well fit with the description of chromoblastomycosis. However, the geographical epidemiology (height, typical soil) makes it less likely, but above mentioned simple microscopic examination should not be left out.

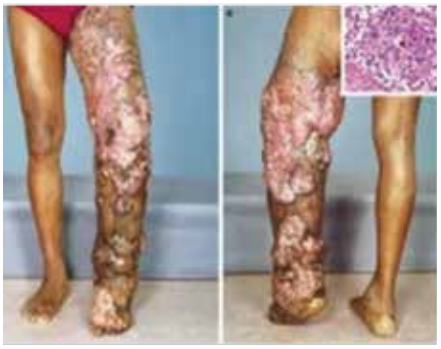

Figure 12. Chromoblastomycosis. Source: www.huidziekten.nl/zakboek/dermatosen/ctxt/Chromoblastomycosis.htm (reproduced with permisson of Dr JR Mekkes).

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Noma, the face of poverty: an old companion of mankind, a medical problem and more

Figure 1. From left to right. Cornelis van de Voorde, a Dutch surgeon who coined the word Noma in 1680, meaning a quickly spreading ulceration; until then, it was wrongly named water canker (with the meaning of a malignancy). Illustration from the first book about noma, Der Wasserkrebs der Kinder (1828) by A.L. Richter; drawings of patients with noma from the concentration camp Bergen-Belsen in World War II.[1]

Noma (also known as cancrum oris) is a quickly spreading orofacial gangrene affecting malnourished children, nowadays mainly observed in tropical countries, particularly in Sub-Saharan Africa, but in earlier ages common all over the world.[1,2] The aetiology of noma is multifactorial. A precondition is malnutrition, often related to poverty, combined with concomitant diseases such as measles, malaria and HIV.

EPIDEMIOLOGY

The global incidence is not known. Estimates range from 30,000 to 140,000 individuals.[3,4] Children with the age of 2 to 7 years are most vulnerable to developing this non-contagious condition, which is most commonly seen in Sub-Saharan Africa. Without antibiotic treatment, the mortality of noma is around 85%. With adequate treatment (amoxillin and metronidazole, hydration and nutritional support, and treatment of concomitant diseases and deficiencies) the mortality rate is reduced to around 15%.[5]

PREVENTION, PRECEDING CLINICAL SIGNS, ACUTE NOMA IN STAGES AND MICROBIOLOGY

Noma is often preceded by a small intraoral ulcer or acute necrotizing gingivitis (ANG), a common finding in poor areas in Africa.[6] A practical approach for prevention of noma is to identify in endemic regions the local communities where ANG is prevalent. An awareness programme among the local population and health workers, with introduction of efficient oral hygiene practice and nutritional support, are the ingredients for a preventive strategy.[7]

The first signs of noma are facial oedema and an almost pathognomonic halitosis. Within a few days, the second phase starts: a rapidly spreading necrotizing infection into the intraoral mucosa, the facial muscles, the skin and the facial skeleton. In this phase, hypersalivation is a frequent symptom. This explains why, in earlier centuries, in many countries

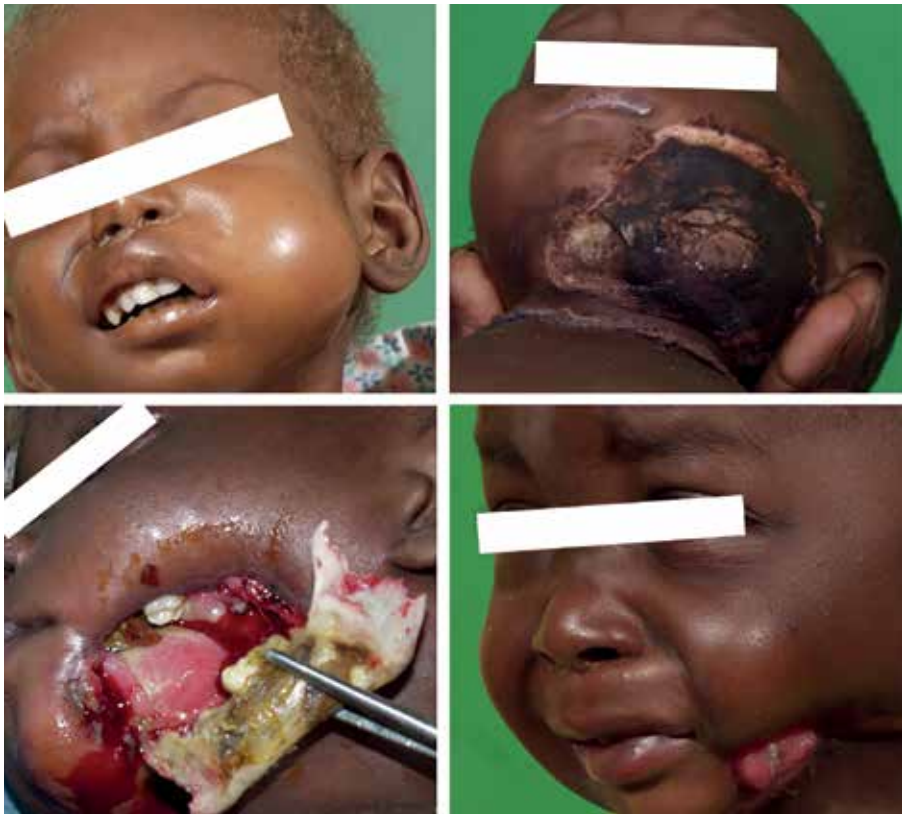

Figure 2. The four stages of noma: facial oedema, demarcation of the gangrene, elimination of necrotic tissue and after secondary healing.

in Europe, noma was called 'water cancer'.[2] Most noma patients die during this septic second phase. In those who survive, one observes that the gangrene becomes demarcated; this is called the third phase. In this phase, the necrotic tissue is eliminated by the body by suppuration, sloughing and sequestration, followed by secondary wound healing (granulation, contraction of tissue, secondary reepithelialisation and remucosalisation), often a process of many months.

Microbiological considerations about noma have changed over time. One century ago, experts expected to find a specific *'bacillus nomae'*. Halfway through the 20th century, bacteria such as *Borrelia vincentii* and *Fusiformis fusiformis* were considered to be involved in the infectious process leading to gangrene. Nowadays, noma is seen as a multifactorial opportunistic infection developing in a relatively normal oral flora in patients with an impaired immune system, caused by factors such as malnutrition and concomitant diseases like measles, HIV and malaria.[8]

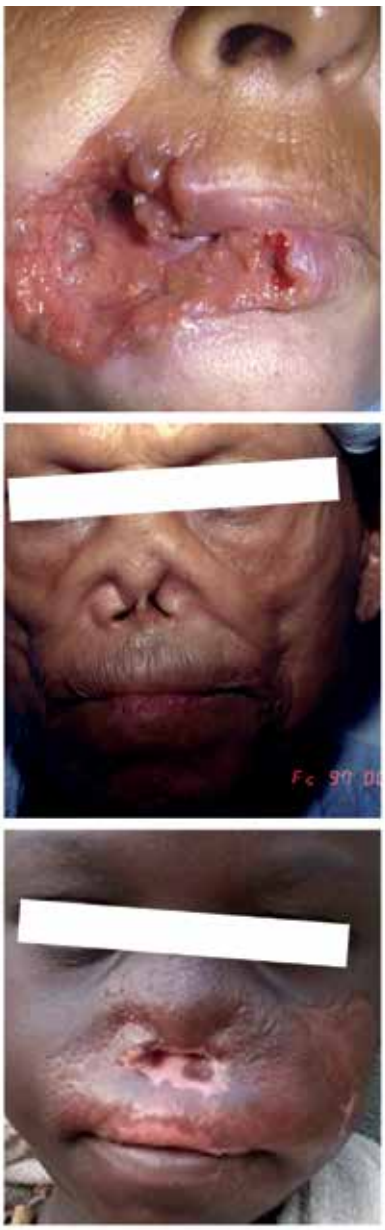

Figure 3. From the top down. Three clinical pictures of diseases that may mimic noma: squamous cell carcinoma, leprosy and skin tuberculosis.

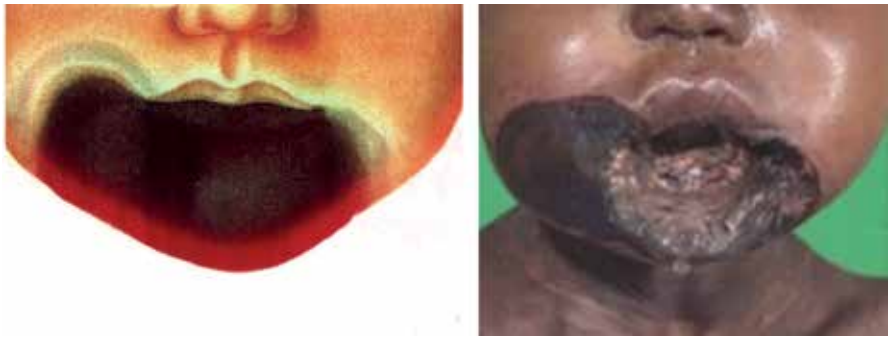

Figure 4. A remarkably similar clinical picture. Left an illustration from Robert Froriep's Chirurgische Kupfertafeln (1844). Right a patient in the Noma Children Hospital in Sokoto, Nigeria in the 1990s. Always different and always the same.

NOMA SEQUELAE AND RECONSTRUCTIVE SURGERY

Depending the extent of the necrosis, the sequelae of noma present a kaleidoscopic variety of facial deformities, often with debilitated function of eating (trismus) and speech, and leakage of saliva as well as social ostracization. Often it leads to further facial deformities due to growth disturbances of the facial skeleton at a later age. Reconstructive surgery in order to treat trismus and improve the aspect of deformed noma faces is only provided by a few Western NGOs in the 'noma belt' of the world, the Sub-Saharan countries, (rarely also in European hospitals), and reaches only a few of the estimated 210,000 noma survivors in the world.[4] Because of the variety of sequelae, noma reconstructive surgery is one of the most challenging parts of reconstructive surgery. It requires thorough experience with all reconstructive operative techniques, an imaginative mind, and high technical skill.[5, 9] Also, intubation of a noma patient sometimes is a difficult procedure, and therefore a challenge for anaesthetists.[10] This should be performed only in the setting of tertiary health care. The surgical adage to keep these procedures 'simple, safe and satisfactory' is valuable. Nevertheless, the postoperative complication rate in noma patients, treated by expert teams, is high.[11] On the other side, the social impact of successful surgical rehabilitation is rewarding, leading to better chances for education, employment and even marriage after surgery.[12]

DIFFERENTIAL DIAGNOSIS

Though Sterling V. Mead, author of *Oral surgery* (1946), commented that concerning the differential diagnosis of noma "there is nothing else like it" [5], there may be patients who present with facial deformities that are very suggestive for noma as cause, but whose mutilated faces have another aetiology like leishmaniasis, leprosy, squamous cell carcinoma, yaws, gangosa, syphilis and trauma.[4,5]

A NEGLECTED 'NEGLECTED TROPICAL DISEASE' AND A MATTER OF HUMAN RIGHTS

Noma is a condition that can be prevented completely by securing food security for the poorest inhabitants worldwide.[1] The fact that the condition still exists on a large scale is a real disgrace to mankind. A prominent feature of noma is omnipresent neglect by medical science, governments of countries where the condition is prevalent, and the World Health Organization. Noma does not appear on the list of seventeen neglected tropical diseases (NTDs), despite data indicating that the global burden of noma, expressed in disability-adjusted life years (DALYs),

is estimated at 1.1 million.[13] Actions by Jean Ziegler, professor in sociology and member of the Advisory Committee of the United Nations Human Rights Council (during 2000-2008), led to the adoption of *Resolution 19/7: the right to food*, with children affected by noma as evidence of a violation of this right.[14]

Noma is an old companion of mankind and will continue to be so, unless mankind takes its humanitarian responsibility seriously.

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Meet your colleagues in global health and tropical medicine

In this new rubric, we would like to introduce you to colleagues in global health and tropical medicine. They could be those who already have considerable experience and are looking back at their career, or those in a much earlier stage of their professional life – basically anyone who has a story to tell. We ask them about:

- their career and motivation to work in global health and tropical medicine
- the insights gained by working in low- and middle-income countries (LMICs) that are useful in the Dutch (healthcare) context
- advice for young professionals
- and finally, a personal book or film tip.

We hope you will enjoy the read and be inspired by our first guest, Klaas Marck.

MEET KLAAS MARCK: AN ADVOCATE FOR NOMA

Klaas Marck is a retired plastic surgeon and the founder of the Dutch Noma Foundation. Until his retirement, he worked at the Medical Centre Leeuwarden, where he established a training in plastic surgery. Next to his medical career, he wrote several books about plastic surgery, especially noma, and his medical missions to LMICs. See also his contribution in this edition of the MT*b* about noma disease.

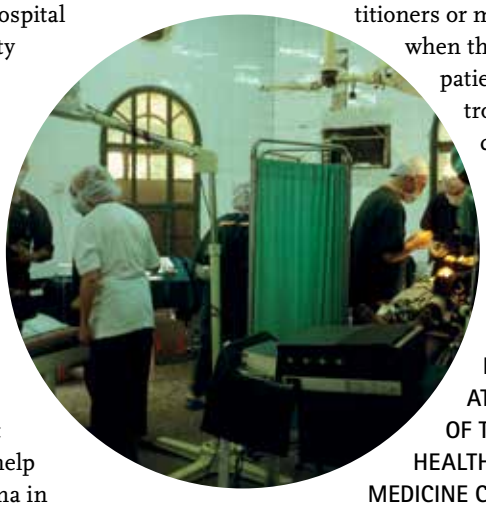
THE INSPIRATION

"The main reason to go to poor regions in the world was to help those in need who would otherwise not have access to surgery. That is why I spent some weeks of my holidays on medical missions. Next to this I have always been curious about other cultures; as a student, I had already travelled the world. I think you need some intrinsic curiosity to work in the places I have been.

A CAREER IN GLOBAL HEALTH

I did my medical internship on Curaçao, which I really enjoyed, and stayed for almost two years. I also worked as an intern in Jamaica and for three months as general practitioner on Curaçao. Part of the pleasure of working in this part of the world was being amongst a mixed population, for a great deal people with an African background. After my army duty, I was trained as general surgeon in the Clara Hospital in Rotterdam and the University Hospital in Groningen. After five years of general surgery, I specialized in plastic surgery in 1983-1986 and started my career as plastic surgeon in Leeuwarden.

My first mission was in 1994 with the German organisation Interplast in an Afghan refugee hospital in the Pakistan city Pesjawar. It was a wonderful time because of the opportunity to gain more surgical experience in a different culture, and extraordinary to work in such a heavily secured setting. Interplast was contacted to help children with noma in Africa, a disease I was not familiar with. Interplast was hesitant to go there, but a friend and colleague of mine asked me to join him to go to Africa and to operate on children with noma. Before going on these missions, I studied and read all I could find about its history, pathology and re-constructive surgery. This extensive study never ended and resulted in the book *Noma, the true face of poverty*. The book details the medical and surgical dimensions of noma, but also its underlying root causes of extreme poverty and food shortages, and the impact on child mortality. Nowadays noma is limited to the poorest regions in the world, but it can happen all over the world. During my literature search, I even found a story of noma after a measles outbreak at the end of the 19th century in Leeuwarden, with only the children of the poorest families suffering from this disease.



The things I am proud of in my global health career include the establishment of the Dutch Noma Foundation, the organisation of many symposia, and the publications on noma and the underlying poverty problems.

INSIGHTS GAINED BY WORKING IN LMICS USEFUL FOR THE DUTCH (HEALTHCARE) CONTEXT

All the experiences in tropical medicine result in good travel advice and even treatment of travellers who go to or return from a tropical country. There should be some hospitals in the Netherlands with a good clinical department of tropical medicine that are known and easy to find by general practitioners or medical specialists when they need to refer a patient with an unknown tropical disease. Those departments already exist, but they should be more visible in the Dutch healthcare setting.

ADVICE FOR YOUNG PROFESSIONALS AT THE START OF THEIR GLOBAL HEALTH OR TROPICAL MEDICINE CAREER

Prepare yourself before you go to a different country. Learn about the epidemiology and the treatment of endemic diseases, but even more importantly about the culture and beliefs of the local people. Also get informed about the hospital where you are going to work, and what the hospital can do for the population. If you are there, pay attention to the untouchables in this other culture. Probably there will be a long waiting line every day at your hospital, and please have a look at the people at the end of this waiting line; these people are the untouchables.

BOOK TIPS

Three books are really worth reading. The first one is *The famished road* written by Ben Okri. It tells the story of a child living in an Arabic culture. The way this child looks at the world and his thoughts about things made me better understand my patients with an Arabic background. The second book is *The wealth and poverty of nations*, written by David Saul Landes. He describes how an economy develops and the influence of, amongst others, the climate on economic welfare, and why people living within the tropics have more difficulty in gaining economic success than people living outside the tropics. The last book is *Ebbenhout* [red.: in English: *Shadow of the sun*] by Ryszard Kapuściński, a poor journalist from Poland working in Africa. Because he could not afford to stay in fancy hotels and restaurants like his European colleagues from richer countries, he stayed among the local people and gained a whole different experience and view than the other journalists. He wrote a couple of books about his experiences in Africa, and *Ebbenhout* is one of them, my personal favourite."

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The books *Noma, the face of poverty* (2003) and its Dutch version *Noma, het ware gezicht van echte armoede* (2001) are still available. They contain a travelogue about the first noma mission in 1996 to Sokoto, Nigeria, an extensive chapter on the history of noma and a state of the art chapter on noma. Also, the book *The surgical treatment of noma* (2006, by Kurt Bos and Klaas Marck) is still available. Readers who want to buy these books should send an email to the author. Each book costs € 10, postal costs excluded.

An outbreak of monkeypox in the Congo Basin

In February 2020, the medical staff of the Congolaise Industrielle des Bois (CIB) hospital in Pokola, a small town in the department Sangha of the Republic of the Congo (Congo-Brazzaville), faced a small outbreak of monkeypox. All cases occurred in the same family of Mbendjele BaYaka, hunter-gatherers living in a small village in the rainforest of the Central Congo Basin, in the neighbouring department of Likouala (Figure 1).

Figure 1. Map of Republic of the Congo and location of the outbreak.

CASE DESCRIPTION

In early February, the mother presented two children to the outpatient department of the hospital in Pokola. Patient A, a previously healthy seven-years-old boy, had a one-week history of fever, dry cough and a sore throat. He developed a rash two days after the start of the fever. Upon examination, a generalised vesicular rash all over the body was seen, including palms of the hands and soles of the feet. Further of note was a generalised lymphadenopathy (Figure 2A, B).

His twenty-year-old sister, patient B, presented with a similar clinical picture that had started a few days later. However, pustules and crusts accompanied the vesicular rash, and the oral mucous membranes and the conjunctivae were affected (Figure 2C). On the sole of the right foot a deeper lesion was noted. Both patients did not appear ill and the fever on presentation had subsided. The mother had no symptoms at all. Thorough history taking did not reveal a bite or scratch of animals, bush meat preparation, or other direct contact with dead animals. However, the mother mentioned that her son (patient A) might have eaten bush meat at another family house.

The third patient, patient C, the five-year-old sister of patient A and B, was admitted one week later with a history of fever for four days, a generalised vesicular rash for one day, loss of appetite and fatigue. On examination, she appeared ill with a temperature of 38°C and was dehydrated. The fourth and fifth case from the family, patients D and E, a sixteen-year-old girl and four-year-old boy respectively, turned up a few days later with the same clinical picture as the first two patients. They did not appear to be ill.

In view of the clinical picture and local epidemiology, the working diagnosis was monkeypox. Other diagnoses considered were chickenpox, scabies and pian (an endemic non-venereal treponematosis). All of these were less likely, supported by the experience of an earlier smaller outbreak in 2019 with an identical clinical picture that had occurred in the Likouala Department. The outbreak was confirmed as monkeypox virus infection by PCR techniques at the Laboratoire Nationale de Santé Public (LNSP) in Brazzaville with the help of the United States of America's (USA) National Institutes of Health (NIH).

CASE MANAGEMENT IN THE HOSPITAL

After admission, all five patients were managed in a separate isolation ward following the *Interim national guidelines for monkeypox outbreak response* of the Nigerian Centre for Disease Control (NCDC) and the Nigerian Federal Ministry of Health.[1] After a refresher training on hygienic protocols and use of personal protective equipment (PPE), a team of nurses previously vaccinated against smallpox was designated to care for the patients. The patients were visited regularly for culturally appropriate psychosocial support by a Mbendjele BaYaka hospital guide. Strengthening nutrition was provided. Clinical management consisted of daily assessment of the patients as well as providing supportive treatment in case of fever, aches and care of the skin lesions. All patients but one had an uncomplicated self-limiting course of the disease, and were discharged when the majority of the skin lesions had crusted (Figure 3). The remaining five-year-old girl, patient C, with dehydration and fever on admission, went through an eventful course with vomiting, bloody diarrhoea, bouts of hypoglycaemia, pneumonia and respiratory distress. Despite intensive medical treatment and nursing care, she died on the tenth day of admission. A safe and dignified burial was carried out.

Figure 2A, B. Clinical picture with vesicular rash in patient A at presentation; C. Rash of patient B at presentation.

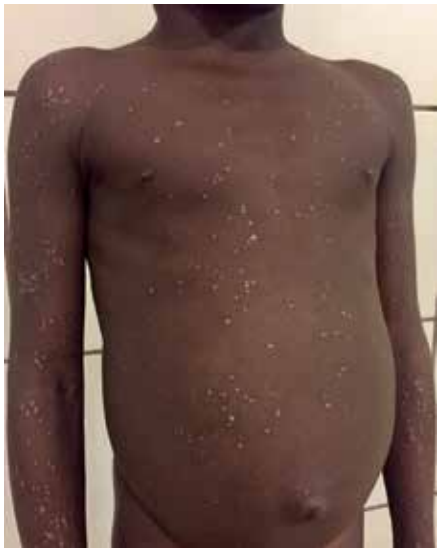

Figure 3. Crusted and healed lesions of patient A upon discharge.

PUBLIC HEALTH INTERVENTION IN THE DISTRICT

The hospital staff organised an outreach to the villages in the area where the disease originated. With the help of facilitators from an NGO experienced in health communication with Mbendjele BaYaka, actions were explained to reduce animal-to-human and human-to-human transmission. With emphasis on the low fatality rate and self-limiting aspect of the disease, the aim was to reduce panic and stigmatisation. Previously trained and well installed Mbendjele BaYaka healers were instructed and provided with pictogrammed education material to ensure continued public health messaging.

BACKGROUND ON MONKEYPOX

Monkeypox is a rare viral zoonotic disease, endemic to West and Central Africa. The causing virus belongs to the Orthopoxvirus genus that includes variola virus (the cause of smallpox), vaccinia virus (used in the smallpox vaccine), and cowpox virus. It was first discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for research, hence the name 'monkeypox'. Human cases were first reported in 1970 in the Democratic Republic of the Congo.[2] An outbreak in Nigeria, ongoing since 2017, is the largest documented.[3] Outside of Africa, from 2003 to date, cases of human monkeypox infections have been documented in four countries: United Kingdom, Israel, Singapore and the USA.[4] These imported cases have all been associated with travel from Nigeria.

The animal reservoir of monkeypox remains unknown. Evidence suggests that it may be rodents and squirrels. Transmission through direct or indirect contact with animals – live or dead animals – including through bush meat consumption, hunting, or trade, is presumed to be the main factor for human monkeypox infections. Human-to-human transmission is less common but possible through close contact with an infected person's skin lesions and large respiratory droplets exhaled during extended face-to-face contact. The incubation period averages between seven to fourteen days. The symptoms, which are usually self-limiting, begin with fever, lymphadenopathy, and myalgia, within a few days followed by skin eruptions, all over the body, with mucous membranes also affected. The rash develops sequentially from macules to papules to vesicles and finally to pustules which crust, dry and fall off. Lymphadenopathy is a key feature that can help to differentiate monkeypox from diseases with similar initial presentation (e.g. chickenpox, measles, smallpox). Case fatality rates range from 1% to 11%, highest with the Central African viral clade and younger children. No specific treatments are available. No vaccine is currently licensed. Observational trials have shown that smallpox vaccines provide up to 85% protection against monkeypox. PCR testing of skin lesion swab or urine sample, and sequencing confirm the diagnosis of monkeypox infection.

Sudden outbreaks with a potentially high transmission risk, such as the one described here, need to be counteracted by public health measures such as case detection, case isolation, appropriate community health messaging and protective measures for health care workers.

CONCLUSION

Monkeypox is a rare viral disease with a low case fatality rate. Increased human-animal interactions are likely to cause (larger) outbreaks in the future. With knowledge of local epidemiology and good clinical reasoning, it can be diagnosed, even if sophisticated laboratory support is not at hand. Protocols from national disease control centres such as the NCDC as well as online local and international consultation are recommended for proper management and public health interventions.

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Acknowledgements
We thank Dr. Jean Vivien Mombouli, Dr. Cynthia Nkoua (LNSP), Dr. Vincent Munster and Dr. Robert S. Fisher (NIH) for the analysis of the monkeypox samples of the outbreak of 2019. We thank Project Bwanga for support with our public health messaging.

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Brucellosis: an ancient pandemic that is still among us

Brucellosis is the most common bacterial zoonosis of livestock, with *Brucella (B.) abortus*, *B. melitensis* and *B. suis* infecting cattle, small ruminants and swine, respectively, as their main hosts, and humans as an incidental host.[1] Discovered in the nineteenth century as Malta fever, brucellosis continues to present veterinarians, public health workers and clinicians with challenges with respect to disease control, prevention, and diagnosis and treatment. The intracellular lifestyle in macrophages and other cells of the immune system, where the pathogen manages to persist indefinitely while suppressing immune responses and shielded from antibacterial treatment, is largely the cause of these problems.

BRUCELLA, THE MASTER OF STEALTH

Brucellosis is an undulating fever that may become persistent and disseminate to any organ, causing severely debilitating disease.[2] *Brucella* bacteria are among the most infectious pathogens requiring as few as 10-100 organisms to cause disease. In animals, *Brucella* replicates most efficiently in the nutrient-rich environment of the placenta. The pathogen is secreted in milk and is present in placental tissue and fluids. Consumption of raw milk and milk products and exposure during assistance with lambing and calving are among the major risk factors for human infection. Infection takes place through the mucosal tissues of the gastrointestinal and respiratory tracts and of the conjunctiva.[3] *Brucella* bacteria that pass the mucosal lining are engulfed by macrophages where *Brucella* escapes lysosomal destruction by creating a unique replicative permissive organelle, the so-called *Brucella*-containing vacuole (BCV). In the BCV, *Brucella* may persist indefinitely, and infected macrophages function as a vehicle for dissemination to other tissues and organs.

BRUCELLOSIS CONTROL, THE TRAGEDY OF POVERTY

Control has been successfully achieved in many countries by mass vaccination, using the effective Rev1 vaccine for goats and the S19 vaccine for cattle (a vaccine for porcine brucellosis does not exist). The World Organisation for Animal Health has strict guidelines for mass whole-flock vaccination and annual or biannual vaccination of all new-borns often being the only option for countries where extensive farming is practiced.[4] Vaccination should be continued for at least the livestock replacement cycle and until the prevalence is below an acceptable level, at which point surveillance with test and slaughter is critical to remove remaining and new foci. From a One Health strategy point of view, systematic reporting of cases at the hospital and in the general practitioners' office may help to focus control efforts. Surveillance by public health workers of high-risk groups, including veterinarians, slaughterhouse workers and milkers, for *Brucella* related symptoms and serological evidence could also be very useful.[5]

Unfortunately, control efforts have failed for almost any reason imaginable, including incomplete vaccination, use of wrong dose, route or timing of vaccination, and no or poor surveillance strategy. For instance, in preparation of a vaccination campaign, a surveillance for bovine brucellosis in districts of South Sulawesi, Indonesia showed 19.3% seroprevalence along with 39% reproductive failure.[6] However, while vaccine would be made available for a single vaccination round, a follow-up strategy was lacking. One of the factors that may complicate the control of *B. melitensis* in particular is the frequent transmission to cattle.[7] Thus when co-herding is practiced (or when goat and cattle use the same pastures or water sources), vaccination of cattle against *B. melitensis* (with S19) needs to be considered to prevent reinfection of goats. In many countries in the Middles East, the Indian subcontinent, Asia and Africa where brucellosis is still endemic, control efforts have been ineffective or not attempted because of the huge (financial) and long-term commitment required.

HUMAN BRUCELLOSIS, A DISEASE IN MASQUERADE

The clinical spectrum of brucellosis includes fever, sweat and constitutional symptoms in most patients. Severe comorbidity such as osteoarticular involvement (sacroiliitis, spondylitis, peripheral arthritis, and osteomyelitis), gastrointestinal presentations (abdominal pain, splenomegaly, hepatomegaly and hepatitis), epididymo-orchitis or neurological, respiratory and cutaneous manifestations may occur as well.[2] The protean manifestations make laboratory testing, preferably by blood culture,[8] and information on risk behaviours and possible exposure indispensable to reach a diagnosis. However, as blood culture requires a specialised laboratory, in practice a variety of serological tests including point-of-care assays is used.[2] Even though effective antibiotics for brucellosis are available, a number of issues have not been solved. The recommended regimens are those combining doxycycline and an aminoglycoside or rifampicin. Of these, the classical combination therapy of doxycycline (for six weeks) plus streptomycin (during the first two weeks) is most effective, with lower relapse and treatment failure.[9] For patients with focal complicated disease, prolonged treatment with or without surgery may be needed. Gentamicin is used as an alternative for streptomycin, but insufficient data is available to support other (double and triple) combination therapies. Shorter courses and single antibiotic treatment should never be used. An all-oral therapy effective in acute as well as persistent localised cases is not available, and definite treatment options for young children and for pregnant or lactating women are not defined.

WHEN DOES DISABILITY WEIGH ENOUGH?

The estimates of disability weights have been proposed to be at least 0.150 for persistent, localised brucellosis and 0.190 for acute brucellosis.[10] The impact of brucellosis in rural and undeveloped areas, where access to medical care is limited and where most patients live, will be most profound. Poor education increases the risk of exposure and limits health seeking behaviour, confounding persistent focal and relapsing disease, and making effective treatment even more cumbersome.[11] Resulting disability has consequences for family income, in particular for farmers who also risk losing their livestock because of brucellosis. Under such conditions, community health education is essential. Health workers may also be involved in active screening of risk groups. A notable risk group may include family members who share the same exposure.[12] Patient support from public health workers is often essential to improve treatment adherence.[13] The devastating effects of brucellosis may be most apparent to public health workers, and the public health service has an important task in keeping brucellosis on the agenda of policy makers.

A TREASURE BUG CONTINUES TO SURPRISE SCIENTIST

Once inside the host cell, *Brucella* rapidly switches gene expression to alter its pathogen-associated molecular signature. A crucial factor is the expression of the bacterial VirB type IV secretory system (VirB T4SS).[3,14] In some other pathogens, such as *Bordetella pertussis*, this secretory system injects a toxin into the host cell. *Brucella* VirB T4SS transports some 15 effector proteins that function to prevent immune recognition, establish and maintain the BCV, support nutrient acquisition, or promote replication etc. Of note is the transport by VirB T4SS of an activator protein (named VceC) of the unfolded protein response (UPP). In eukaryotic cells, UPP safeguards the proper folding of newly synthesised proteins and may activate a process called programmed cell death (apoptosis) when unfolded malfunctioning proteins accumulate. Activation of UPP by VceC appears crucial for *Brucella* to maintain infection, as UPP activation is essential for replication and nutrient acquisition and promotes cell-to-cell spread. Apparently, through the VceC effector molecule, *Brucella* manages to alter and use UPP to safeguard infection and to live its hidden, stealthy life.

CONCLUSION

Tools to diagnose, treat, prevent and control brucellosis may not be perfect but have proven to significantly reduce the disease burden. Unfortunately, as a disease of poverty that tends to generate poverty, interest in brucellosis is declining and the economic and public health impact is underestimated and not ranked high enough on the long lists of priority diseases to compete with the more fashionable diseases of affluence. The need for a long-term assignment with a significant investment is the main barrier that prevents endemic countries from developing and implementing control efforts.

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Patients in the waiting room of a clinic in the high Andes in Peru with behind them an information poster on zoonotic diseases giving attention to brucellosis.

Histoplasmosis: a short overview

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*. Inhalation of spores causes the infection, which occurs especially in people disturbing soil that contains bird or bat droppings, but is also reported in travellers after visiting caves or guanos.[1,2] After inhalation, the body temperature transforms the spores into yeast cells which in turn spread to lymph nodes and the bloodstream. Histoplasmosis does not spread between people and animals or between infected people. *H. capsulatum* and its variants are distributed throughout the world, especially in the Americas, followed by Africa, Asia and Australia. *H. capsulatum var. duboisii* is the larger uncommon African variant causing extrapulmonary manifestations but treated similarly (Figure 1).

The true incidence of histoplasmosis is difficult to determine, but the majority of cases occur in North and Latin America, with around 6.1 cases per 100,000, and even outnumbering the deaths from tuberculosis. Although in Italy there have been some endemic cases, histoplasmosis is extremely rare in Europe and is mainly imported by migrants and travellers. Hence, most (European) physicians are unfamiliar with this disease. The difference in geographic distribution is caused by variations in soil composition (vegetation) and climate.[3,4] Although the period of incubation ranges from three to seventeen days, diagnosis has been described up to forty years after exposure in an endemic region.[5] Quite similar to *Mycobacterium tuberculosis*, and often difficult to distinguish, *H. capsulatum* can remain in a quiescent state until the cell-mediated immunity is compromised.[6]

GLOBAL BURDEN OF HISTOPLASMOSIS

In 2017 the World Health Organization broadened the list of neglected tropical diseases with deep mycoses, of which histoplasmosis is one. Despite its endemicity, the global burden of histoplasmosis is not well documented. It was Charles Darwin who first described histoplasmosis in the Panama Canal Zone in 1906, reporting patients with features of disseminated tuberculosis. Nowadays, the spread of HIV together with the increasing use of immunosuppressive drugs, for example in chronic inflammatory diseases or after organ transplantation, are major risk factors for histoplasmosis. Already in 1987, disseminated histoplasmosis was classified as an AIDS-defining infection, but histoplasmosis still remains as under-recognized and misdiagnosed as tuberculosis. Historically, prevalence mainly manifested itself in North and South America. However, in the African continent, the incidence of histoplasmosis increases with the burden of the HIV/AIDS epidemic. However, both diagnosis and treatment are difficult because of costs and lack of materials or trained personnel. Worryingly, intravenous amphotericin B, the first-choice

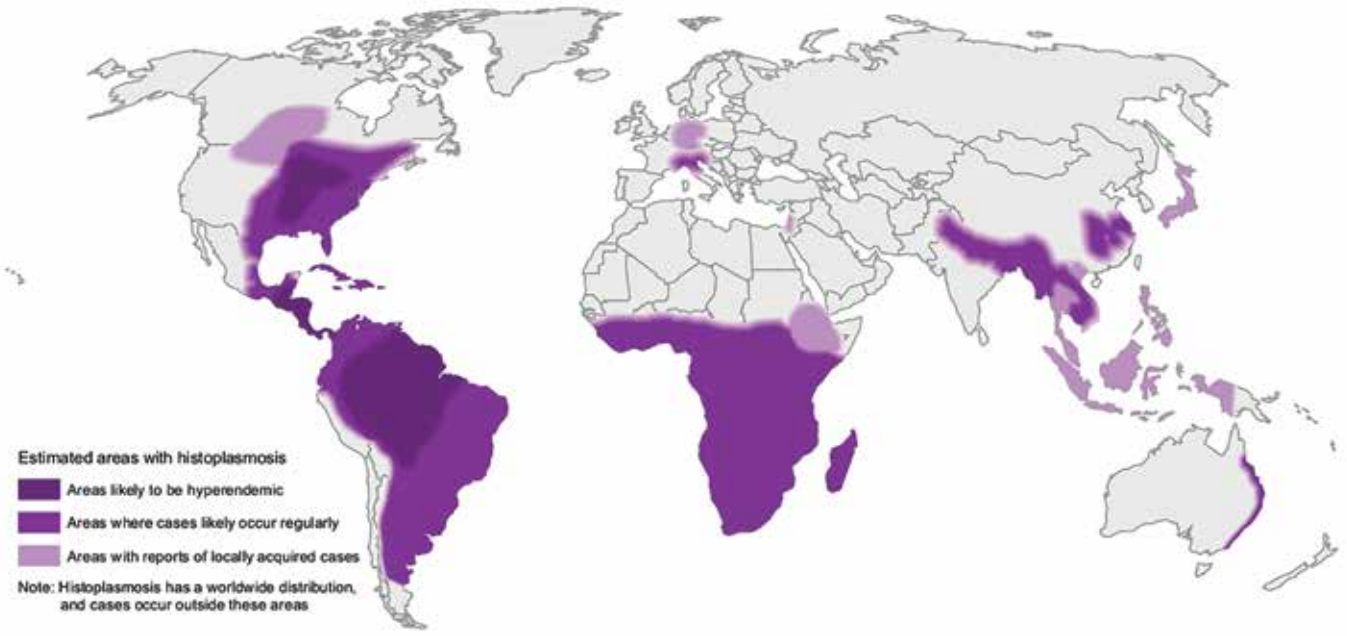

Figure 1. Map showing the distribution of histoplasmosis around the world.[8]

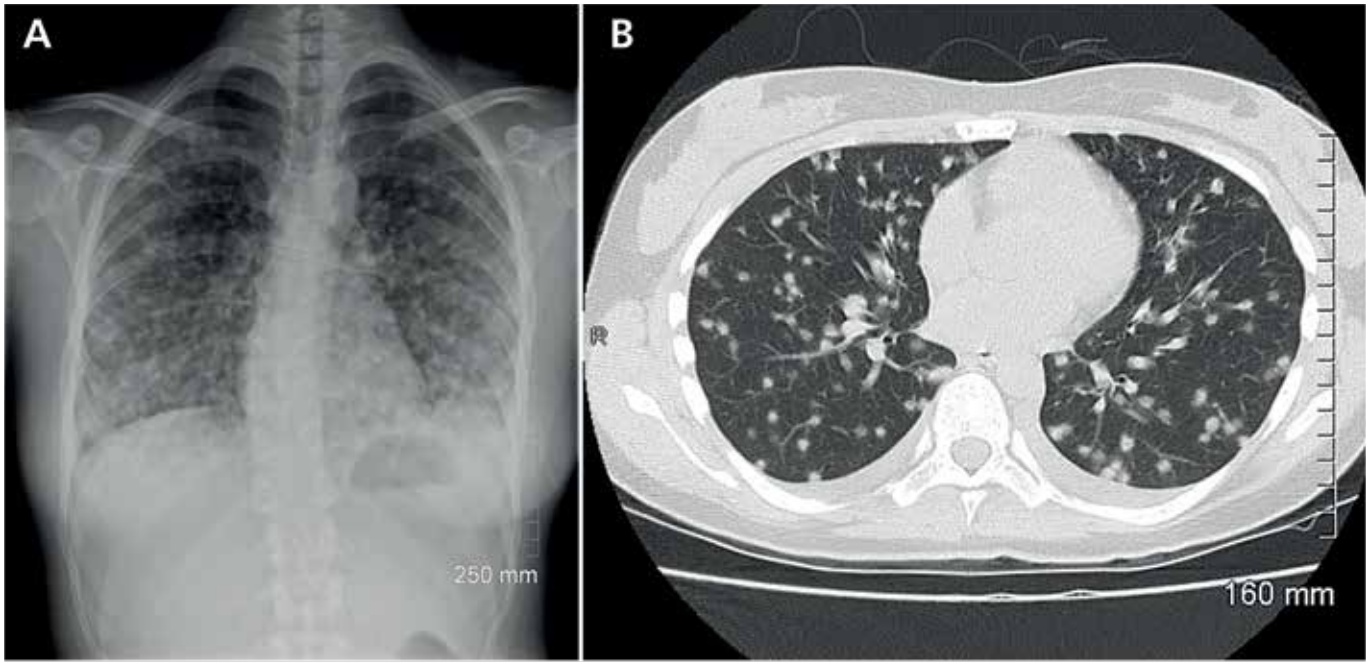

Figure 2. Extensive bilateral nodular lesions in the lungs caused by histoplasmosis on a chest X-ray (A) and a CT scan (B).

antifungal therapy in disseminated disease, is not licensed or is unavailable in a number of African countries.[7]

CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT AND PREVENTION

In most patients, infection is asymptomatic, but it may lead to disseminated histoplasmosis, a life-threatening illness. Upon infection, patients usually present themselves with pulmonary complaints (Figure 2). A more general presentation with malaise, fever, myalgia, rheumatic manifestations or even central nervous system histoplasmosis may occur. Diagnosis is confirmed by a positive culture or, more rapidly, by antibody or antigen testing.[6] Because histoplasmosis is known to mimic other diseases, the risk of exposure is an important clue to raise the index of suspicion. The recently published systematic review by Antinori et al. described that progressive dissemination was mostly seen in HIV positive patients, but that the worst outcomes were seen in HIV negative immunocompromised subjects, with a mortality rate of 32%.[5] Treatment options include intravenous amphotericin B or oral itraconazole. The latter is recommended by the Infectious Diseases Society of America as prophylactic therapy in HIV positive patients in highly endemic areas. The duration of treatment depends on the severity of the disease.

CONCLUSION

Histoplasmosis is a neglected tropical infection. Even outside of endemic regions it is important for physicians to recognize and manage this disease, particularly in view of the worldwide migration patterns and global travel.

©

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Myiasis

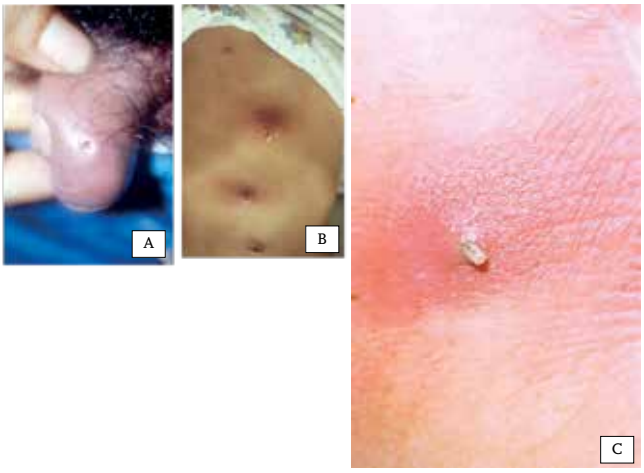

Figure 1A. Myiasis on the shaft of the penis, and, B, on the buttocks.
Figure 2. Myiasis in a baby.
Figure 3. The rear-end of the maggot is in the air to enable breathing of the maggot.

Most of us have experienced the patient's panic: "Doctor, something is moving under my skin!" (Figure 1-3). The diagnosis of myiasis is easily made by those who are familiar with it, but many are not. Myiasis is a parasitic infestation of the skin with live larvae of a variety of fly species. It affects both humans and animals. It is more commonly seen in the tropics and is uncommon in temperate regions.[1,2] The parasite is usually seen in tourists after returning home; in low- and middle-income countries (LMICs) it may affect people of all socio-economic classes; many are familiar with the condition and do not report to a health facility unless there are complications. The true prevalence is not known. Myiasis (derived from the Greek *myia* = fly) refers to the invasion of human or animal tissues by the maggots of flies. Different body parts may be involved, resulting in different clinical classifications, e.g., wound, cutaneous, dermal, traumatic, gastric, rectal, and genitourinary myiasis. The larvae feed on tissue (live or dead), or in the case of intestinal myiasis, on ingested food.

Human myiasis can present as:[1,2]

- Obligate or mandatory – here, myiasis refers to true parasitism, where part of the developmental stage of the larvae is spent in living tissue. Most commonly, this occurs in animals such as sheep, cattle, and horses, but the invasion of human tissue by the human botfly in Central and South America and the mango fly in Africa has been well documented.
- Optional or facultative – myiasis occurs when larvae invade living tissue after lodging in nearby, organic, or decaying tissue in a wound.
- Accidental – myiasis (pseudomyiasis) refers to larvae found in the gut or urinary tract. These larvae are usually accidentally ingested with food. There is no obligate intestinal dipterous parasite of humans. Although usually a benign event, abdominal pain, nausea, and vomiting can result from accidental myiasis.[1,2]

TRANSMISSION

Many different fly larvae (maggots) are involved in myiasis; identification can be complex and requires an entomologist. The causative agent of myiasis varies between geographical regions: the bot fly *Dermatobium hominis* is most frequent in the Americas, while in Africa the blow fly *Cordylobia anthropophaga* is the most common. Symptoms caused by the maggots of these different fly species are similar.

D. HOMINIS

The size of the *D. hominis* fly is 12-18 mm; it is densely haired and looks like a bumblebee.[3] It occurs in the neotropical regions of the New World, from southern Mexico to northern Argentina, where temperature and humidity are relatively high, in mainly lowland forests, especially in trails along forest and scrub. It is particularly important as a cause of myiasis in cattle in Brazil.[1,3,4]

The female fly sticks approximately 6-30 eggs on to the body of other insects such as day-flying mosquitoes, blood-sucking flies and even ticks, which then serve as vectors to carry the eggs to the host (a process known as phoresy). The female fly deftly grabs the insect vector in mid-air and deposits eggs on its abdomen. Embryos begin to develop into first instar (the first stage in development) larvae but refrain from hatching until the vector lands and feeds on a potential host. The larvae then emerge and within ten minutes burrow into the dermis and take two days to reach the subcutaneous tissues. This results in furuncle-like skin lesions with an opening, through which the larvae breathe (Figure 2). The development lasts approximately 40-60 days, after which the larvae emerge, drop to the ground, and pupates.[1,3]

C. ANTHROPOPHAGA

This blow fly occurs in Africa and is often called the putzi, tumbu or mango fly. It belongs to the family of blow flies that frequently cause furuncles that may coalesce, and plaque formation. Adults are relatively large (9-12 mm); they are stout, compact flies with a yellow to light brown colour and two dark gray, ill-defined dorsal longitudinal thoracic stripes.[1,5]

C. rodhaini (Lund's fly) is the only other *Cordylobia* species known to infest humans. It has a limited distribution in Africa, mainly the tropical rainforests. It often causes more than one lesion, leading to extensive furuncular myiasis.[1,6] Females of all *Cordylobia* species can lay up to 100-300 white banana-shaped eggs on sand or soil in shady areas, especially if contaminated with urine or faeces such as baby's diapers as well as laundry drying outside in the sun. The larva uses its powerful oral hooks to quickly penetrate the skin, leaving only the rear part of its abdomen in contact with the air (Figure 3). When development is complete (usually within 7-14 days) it

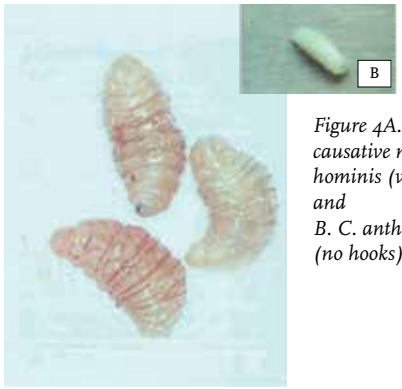

Figure 4A. The causative maggots of D. hominis (with hooks), and B. C. anthropophaga (no hooks).

Figure 5 A-D. Removal of the maggot. After application of Vaseline™ the maggot seeks air and moves to the surface of the skin

leaves the host and falls to the ground, where it buries itself and pupates.[1,5]

CLINICAL FEATURES, DIAGNOSIS AND TREATMENT

OBLIGATE OR MANDATORY MYIASIS

This is a zoonosis caused by *D. hominis* and *Cordylobia* species; humans are not accidental hosts. The most common clinical form is the furuncular form, in which a boil-like lesion develops gradually over a few days. After infection, there may be mild constitutional symptoms. Each lesion has a central punctum, which drains serosanguinous fluid. The larva quickly burrow itself into the skin, but leave its posterior end, which contains a group of spiracles, in direct contact with the air. The movements are usually noticed by the patient, as is the associated pain. Lymphangitis and regional lymphadenopathy may result from the associated inflammatory response; eosinophilia may be found in the blood. Once the larva has emerged or is removed, the lesions quickly disappear.[1,2]

DIAGNOSIS

The diagnosis is usually supported by the travel history, the presence of boil-like lesions in which the patient feels movement, and lack of response to antibiotic treatment (Figure 3).[7,8] Ultrasonography may be helpful.[9] The differential diagnosis includes staphylococcal skin infections, cat-scratch disease, insect bites, tick-bite granuloma, inflamed cysts and tungiasis.[1] It is important to identify the larvae and determine whether they are facultative or obligate parasites. They are best killed by immersing it in very hot (>80C°), and then preserved in a solution of 70-95% ethanol. Formalin solution should not be used for preservation as it causes hardening of the larval tissue, which adversely affects processing (Figure 4 A,B).[12]

TREATMENT

The maggots can sometimes be expressed by firm pressure around the edges of the lesions, but the punctum may require surgical enlargement. This doesn't work so well for the *D. hominis* larva, which has a bulbous tip and is equipped with rows of backward-facing spines. Traditional methods of treatment include sealing the punctum with pork fat, which blocks the larva's breathing hole and encourages extrusion.[13] The same principle can be achieved with mineral oil, petroleum jelly (Vaseline™), butter, or a transparent occlusive dressing (Figure 5 A-D).[14] Occlusion may be less effective in the advanced stages of the infestation; surgical treatment is then the preferred choice. The lesions are hardly ever infected, therefore in general antibiotics are not needed.

OPTIONAL OR FACULTATIVE MYIASIS

Fannia canicularis (small house fly) and *Musca domestica* (house fly) can lay their eggs in wounds, ulcers, and moist areas, giving rise to facultative myiasis in wounds and urogenital myiasis. Urogenital myiasis occurs when ovipositing flies lay their eggs near genital orifices, through which larvae enter the genital tract, causing pain, and larvae may be found by accident in the urine (accidental myiasis).[1]

Clinical features depend on the localisation. Facultative myiasis is not an uncommon complication of wounds in LMICs. While these are commonly traumatic, these also occur in patients with leprosy or elephantiasis (caused by lymphatic filariasis). Wounds that are exposed (not covered) in hot weather are most at risk. The larvae (maggots) can be seen, sometimes in large numbers, in the purulent tissues, and their removal of necrotic tissue and beneficial effect on granulation has led to their use in maggot debridement therapy.[15,16] The difficulty is in containing them in the wound as some maggots prefer healthy granulation tissue.

THERAPY

Debridement and irrigation should be done with treatment of secondary infection.[17] Ivermectin has been used in wound infestation (topical and oral) and in the management (oral) of cavitary myiasis, such as aural or nasal infestation, where manual removal of larvae is painful.[18]

PREVENTION

Prevention is by sleeping in-doors, window screens, repellents, protective clothing, and sanitation. Laundry should be ironed as this kills the larvae. Wounds need to be cleaned and covered.

ACCIDENTAL - MYIASIS (PSEUDO-MYIASIS)

This form of myiasis can be related to accidental ingestion of eggs or larvae on contaminated food or water. Symptoms of accidental myiasis are nonspecific. Usually there is abdominal pain, nausea, and rectal bleeding, as well as toxigenic or bacterial gastro-enteritis.

The diagnosis is by clinical suspicion. Larvae can be observed in stool specimen examination. Treatment with oral ivermectin could be tried but nonspecific supportive measures are more helpful.[1] Prevention is also here most important. Exposed food should be discarded, and fruits and vegetables should be washed prior to consumption. Meat should be fresh and free of eggs and larvae.

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Tungiasis

Tungiasis is a common condition in the tropics, also known as sand flea disease or jiggers. It is caused by the penetration of the female sand flea *Tunga penetrans* into the epidermis of its host. It is a huge problem in neglected areas where affected persons, particularly children, can develop pain and deformities of the feet that lead to difficulty in walking. Tungiasis is often treated at the level of local healers and most patients are familiar with the condition. It is only seen by doctors or by dermatologists when it occurs in the higher socio-economic class, or in tourists who do not know the condition and have terrible itching. Although patients and local healers know how to treat the condition, complications such as bacterial superinfection can occur that require medical care.

EPIDEMIOLOGY AND RISK FACTORS

Tungiasis is found on the American continent, from Mexico to northern Argentina, on several Caribbean islands, and in almost every country in Sub-Saharan Africa. In endemic countries, the distribution of tungiasis is uneven and usually occurs in foci. Typically, these are urban squatter settlements, traditional villages along the coast, or underdeveloped communities in the rural hinterland, often in places rarely visited by the mainstream tourist.[1,2] Tungiasis is a zoonosis that affects a wide variety of domestic and wild animals. Depending on the setting, dogs, cats, pigs, and rats are the main reservoirs for the sand fleas.[3,4]

The condition is considered a neglected disease of marginalised populations. In resource-poor communities, the prevalence can be as high as 60%.[5] Individuals can harbour between a few to more than a hundred sand fleas.[6] There is a clear seasonality in the incidence of new

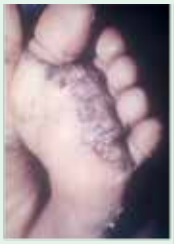

Figure 1. Chronic tungiasis.

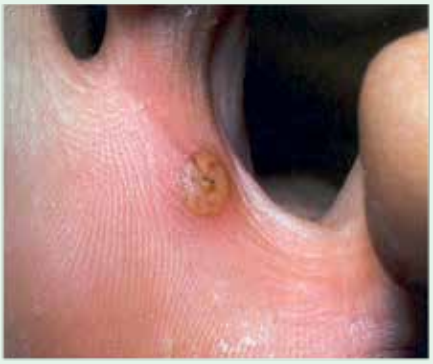

Figure 2. Stage III tungiasis.

Figure 3. The abdomen of the sand flea is freed.

Figure 4. Tunga penetrans after extraction.

penetrations, with little occurrence during the rainy season and a high attack rate during the dry season.[1,8]

While sandy soil and the beach is where most tourists become infected,[9] sand fleas also reproduce easily on any other type of soil, in banana plantations, and in compounds. Even dust-filled crevices in a floor are suitable sites for host propagation, provided there is some organic matter for larvae to feed on and the soil temperature is high enough to allow development of the egg into an adult flea.[1,4] The infestation with the sand fleas occurs when walking barefoot or when bare skin touches the ground where adult sand fleas are present: on a beach, on unpaved paths, around the houses in a compound, or in houses without a solid floor.[4] After a sand flea has found a suitable site, usually the toes, under the nails, between the sole and the toes, the heel, or the lateral edge of the foot, it invades the stratum corneum and is even fully entrenched in the epidermis in less than thirty minutes to a few hours.[2] The penetration process is usually not noticed.[1]

PATHOPHYSIOLOGY

Once the sand flea is embedded in the stratum corneum of the skin, the flea undergoes development, causing the abdominal segments to enlarge to the size of a pea, loaded with eggs. Hundreds of eggs are released through a minimal opening in the skin in a period of about three weeks.[1,2] After the eggs are released, the involution of the expanded abdomen begins. Three to four weeks after penetration, the parasite dies and is eventually removed from the epidermis by the tissue repair mechanisms. Tungiasis is a self-limiting condition.[1,2]

However, in poor individuals living in endemic areas reinfection is the rule, and its consequences are common. Repeated infection leads to chronic inflammation of the feet with persistent pain and difficulty in walking (Figure 1).[6] In these settings, tungiasis can lead to significant morbidity and impairment in quality of life.[7] Because it is relatively rare among tourists and the local middle-to-upper class, the condition is often misdiagnosed, and patients are subjected to inappropriate therapeutic procedures.[1,2]

CLINICAL FEATURES

It is important to realize that tungiasis is a dynamic process.[10] Consequently, the macroscopic appearance of tungiasis depends on the stage of the maturing flea. Based on clinical and morphological criteria, the natural course of tungiasis can be divided into five stages:[1,2,10]

- Stage I (flea in *statu penetrandi*, thirty minutes to several hours). A small reddish spot of about one millimetre appears with or without an erythematous halo.
- Stage II (onset of hypertrophy, 1-2 days after penetration). The lesion becomes more apparent as a growing papule develops. The protruding back of the flea with the anal-genital opening appears as a central black dot surrounded by erythema. At this stage, there may be severe itching, especially in patients exposed to the parasite for the first time.
- Stage III (maximal hypertrophy, two days to three weeks after penetration). The hypertrophy becomes visible macroscopically. A round elevation with well-defined edges and tight consistency appears, frequently surrounded by desquamation. Eggs and faeces production is typical at this stage, and the lesion is painful (Figure 2).
- Stage IV (3-5 weeks after penetration). A black crust covers an involuted lesion with a dead, decaying parasite. At the end of this stage the carcass of the ectoparasite disappears from the epidermis resulting in a circular impression in the skin.
- Stage V (six weeks to several months after penetration). Characteristic is the stamp-shaped imprint in the stratum corneum (Figure 1).

In persons who are repeatedly infected, the lesions will be in one of these five stages. This natural history of sand flea disease may be complicated by bacterial superinfection and manipulation of the lesions by the patient or his caregiver. Bacteria are either introduced into the epidermis by the invading flea or introduced by scratching or attempting to remove the flea with a non-sterile instrument. In endemic areas, bacterial superinfection is present in almost all

cases, while it is less common among tourists.[4,11] Superinfection leads first to a micro abscess, then to a pustule, and finally to suppuration. *Staphylococcus aureus* and streptococci are the most common micro-organisms isolated, but other aerobic and anaerobic bacteria (including *Clostridiae*) are also found.[11] Importantly, this can lead to tetanus in unvaccinated individuals.

Pathogenic micro-organisms can enter the circulation as the parasite's proboscis is inserted into a capillary of the dermis. If the flea is removed with a sharp instrument such as a needle, nail, or thorn, it leaves a small wound that easily becomes superinfected. When the parasite ruptures during manipulation or if the mouth part remains in the dermis, a foreign body inflammatory reaction may develop.[1]

DIAGNOSIS

The diagnosis of tungiasis is made clinically. For tourists and individuals not living in endemic areas, the travel history is of importance. The patient complains about severe local itching, pain, and the sensation of something in the skin. The presence of two or more identical lesions at the toes, particularly along the nail rim, is diagnostic. The observation of eggs being expelled or attached to the skin around the lesion and the release of brownish threads of faeces are pathognomonic signs. The use of a dermatoscope is helpful.[12] Expulsion of eggs can be provoked by massaging the hypertrophy zone slightly. While the feet are predilection sites for tungiasis, one should be aware that other parts of the body can be involved too.[1] The differential diagnosis differs according to the stage. Skin biopsy is hardly ever needed.

TREATMENT

Surgical extraction of the flea under sterile conditions is still the only reliable treatment. The opening in the epidermis must be widened until the abdomen is completely freed (Figure 3). Then the entire flea must be carefully taken out with tweezers (Figure 4). After the extraction of the parasite, the wound should be treated with an antiseptic or, according to some, with a topical antibiotic. The tetanus immune status must be checked. A randomised controlled trial has shown that oral ivermectin is not effective in the treatment of tungiasis.[13] However, there is sufficient evidence supporting the use of occlusive agents, especially dimeticone-based products.[14,15]

PREVENTION

Wearing socks and closed shoes protects to a certain degree. Daily inspection of the feet and immediate extraction of embedded fleas prevents complications. A twice-daily application of a repellent based on plant extract (jojoba seeds) in coconut oil (Zanzarin®), reduced the infestation rate in an area with an intense transmission by almost 90%.[16,17] If applied regularly, it protects effectively against invading sand fleas, even if no shoes are worn. Unfortunately, for children in low-income countries this is at present still a dream. Commercial Zanzarin® is not produced any more, but it can be made locally.

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When the sun is your enemy: harsh life of albinism and xeroderma pigmentosum patients in the tropics

Countries in the tropics receive sunlight that is more direct than in the rest of the world, but most people who live in these areas have a pigmented skin that offers protection against the sun's harmful rays. There are however congenital disorders that greatly increase an individual's sensitivity to ultraviolet (UV) light. For people suffering from these conditions, life in the tropics can be extremely cruel. They can easily get sunburnt and are at risk of severe actinic damage and skin cancer. The prevalence of two autosomal recessive genetic conditions, oculocutaneous albinism (OCA) and xeroderma pigmentosum (XP), might be low globally but can in some tropical countries be relatively high.[1,2]

Early sun protective interventions and treatments in photosensitive patients have a positive impact on morbidity and mortality.[1-3] It is therefore crucial that they are diagnosed with the condition and treated as soon as possible.

SUN EXPOSURE AND DEVELOPMENT OF SKIN CANCER

Figure 1 shows a simplified but useful model of photo-carcinogenesis. UV exposure causes DNA damage in the skin cell. This leads to mutations and eventually uncontrolled growth, skin cancer. There are acquired and inherited factors that block UV-exposure to cells. These include pigmentation, thickness of the skin and hair growth. Persons with albinism (PWA), have a complete absence or decreased biosynthesis of melanin and are therefore highly susceptible to DNA damage.[1,4,5]

Complicated repair pathways, especially the nucleotide excision repair (NER) mechanism, eliminates damage before it causes mutations. NER is a process in which DNA structural anomalies are recognized, removed and replaced by correct DNA. Patients with XP have a deficiency in NER and as a consequence develop multiple cancers, often starting from a very young age.[2,3]

Finally, mutations can be identified and attacked by a healthy immune system before they develop into skin cancers. This explains why people with an impaired immune system, such as HIV-patients or patients on immunosuppressive drugs (e.g. organ transplant recipients), have an increased risk of malignancies.

OCULOCUTANEOUS ALBINISM

Persons with albinism have a normal amount of melanocytes in the epidermis but these are dysfunctional, causing total or partial absence of melanin pigment in skin, eyes and hair. This predisposes individuals to actinic damage and eventually full-blown skin cancers. These patients also frequently suffer from ocular pathology, reduced visual acuity, photophobia and refractive errors.[1,5]

The most common known types are classified as OCA types 1 (A and B) to 4. The global incidence of albinism is 1:20,000 individuals, but there are certain areas with much higher estimated rates like the indigenous Guna Yala (Panama and Colombia) 6.3:1,000 and Tanzania 1:1500. OCA-1 is most commonly found in Caucasians; OCA-2 is the prevailing subtype in Africa.[1]

Persons with albinism are not only physically disadvantaged; their distinctive features can also create psychosocial problems. Lack of understanding of the genetic cause of OCA generates a widespread belief in 'magical powers', as people wonder how it is possible that two dark skinned people can be the parents of a white child. An indeterminate number of PWAs have been persecuted and become the victims of brutal attacks and murder in the name of witchcraft, superstition and wealth. Various crimes against them have been reported such as infanticide, kidnapping, amputations and decapitations, committed for purposes of supplying highly valued body parts used for amulets. This results in PWAs living in a constant state of guilt and angst, hiding out of fear, and with restricted social integration into the society.[4,6]

XERODERMA PIGMENTOSUM

In a population where most individuals have a coloured skin, it is usually not difficult to identify a baby born with OCA, due to the clearly distinctive 'fair' skin. However, the situation is quite different with XP patients, who are usually born without visible abnormalities. Their skin soon becomes dry and scaly with multiple lentigines.[2]

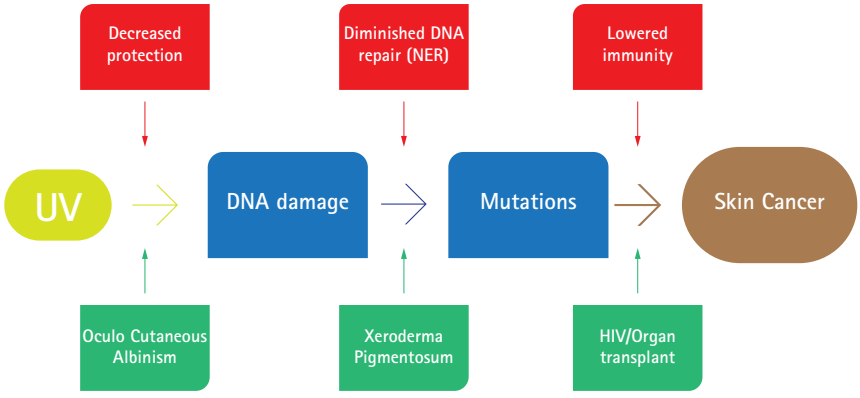

Figure 1. The process of photo-carcinogenesis: failing protection (red) and associated medical disorder (green).

Figure 2A. Almost total absence of melanin in an African boy suffering from OCA-2; B. Red-bronze skin colour, rufous albinism in a young African girl with OCA-3.

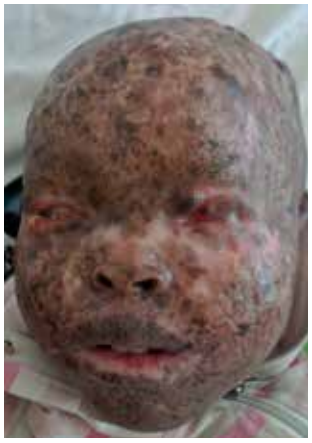

Figure 3. Large squamous cell carcinomas can arise in severely actinic damaged skin.

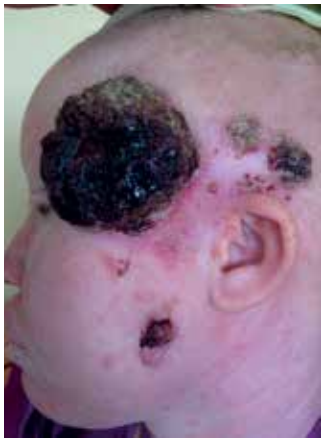

Figure 4. The dramatic sun damage to skin and eyes in a patient with impaired DNA repair present early in childhood.

Seven genetic subtypes of XP, so called complementation groups (XP-A through to XP-G), have been identified, based on different mutations in the NER pathway. The mutation related dysfunction can affect recognition of the DNA damage, the unwinding of DNA strands, or the replacement of abnormal sections by the proper nucleotides. Although these complementation groups slightly differ from each other phenotypically, with a minority of patients also suffering from neurological abnormalities, extreme sun sensitivity of skin and eyes is a common feature. Depending on the amount of UV exposure, XP patients develop actinic damage with severe scarring of the skin and conjunctiva and eventually multiple cancers. They have a nearly 10,000 times higher risk of developing nonmelanoma skin cancer (basal cell carcinomas and squamous cell carcinomas) and 2,000 times higher risk of melanomas. About 20% of XP patients develop a tumour on the tip of the tongue that can be malignant squamous cell carcinomas or benign pyogenic granulomas.[2]

Xeroderma pigmentosum in the global population is very rare; rates in Europe and the United States of America are estimated to be around 2.3 per million inhabitants. In populations where consanguinity is more common, the numbers are much higher. Northern and Sub-Saharan Africa and the Middle East have a much larger incidence of XP-C in particular. The most common complementation group in Japan is XP-D; prevalence there is thought to be about 1:22,000 inhabitants.[1]

MANAGEMENT

The relatively high number of PWAs in particular but also of XP patients in some tropical countries emphasizes the need for awareness and the availability of interventions to address the medical, psychological and social needs of such vulnerable populations.[4] Treatment therefore requires a multidisciplinary approach, including dermatologists, ophthalmologists, surgeons, pathologists, specialized nurses, psychologists and social care health workers.[2] Management in most tropical countries would, however, unfortunately be very challenging due to financial, infrastructural and sometimes socio-cultural circumstances.[4] Still there are some great initiatives aimed at improving the life of these patients. A good example is the Regional Dermatology Training Centre (RDTC) in Moshi, Tanzania, which runs a thriving outreach project with a mobile skin care clinic for PWA and XP patients.[5,8] They also produce their own sunscreen (Kilimanjaro suncare®).[2]

As is evident from Figure 1, the risk of skin cancer is proportional to the accumulated amount of UV radiation absorbed by the skin cells (keratinocytes). It is therefore of utmost importance to limit sun exposure as much and as soon after birth as possible. Personal protection can be achieved by wearing a wide brimmed hat, using sunglasses, and frequently applying sun protection cream (SPF 50). An UV-blocking visor, if available, should be worn during daylight exposure, and outdoor activities are preferably performed from dusk to dawn.

A successful implementation of protective measures can only be achieved if patients and their family and community are truly aware of the benefits of these. Health education is therefore very important. The RDTC uses fellow sufferers for education and instruction, as it is thought to be more likely that the patient will accept and follow their advice.[4,7,8]

Immediate treatment of pre-malignancies will reduce the risk of progression into invasive carcinoma. Different modalities can be used including cryotherapy, photodynamic therapy, and the combination of curettage and coagulation. The use of tumour-protective oral retinoids (acitretin and isotretinoin) has been shown to be beneficial in some cases. Of course, one should be aware of the adverse effects of these medicines in young patients, especially skeletal abnormalities and inhibition of growth due to premature epiphyseal closure. Studies have proven the use of topical ointments as a field directed therapy, including 5-fluorouracil and imiquimod. This can be particularly helpful for larger areas of dysplastic skin. Larger tumours are preferably

Figure 5. Liquid nitrogen is a simple and usually effective treatment option for pre-malignancies.

removed by excision. A pathologist who is experienced in dermatological pathology is another requisite to examine the margins of the excised tumour for total removal. Radiation therapy seems not to be a first-line treatment and should only be reserved for inoperable tumours.[2,3]

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Note by the author
Some of the photographs in this article have been previously used in other publications by the same author R.K. Horlings. These photographs have been taken by the author, courtesy of the Regional Dermatology Training Centre (RDTC) in Moshi, Tanzania.

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ANNOUNCEMENT

Global health knowledge transfer: the time is now

Global health (GH) challenges can be found all over the world. So can ways to address them efficiently and sustainably. Kennis (knowledge) Connectors Global Health (KCGH) aims to tap into GH insights and make them actionable for the Dutch health system. So how does this knowledge transfer platform facilitate the capture, transformation and sharing of knowledge by GH professionals?

APPLYING GH INSIGHTS IN THE NETHERLANDS

A global perspective is vital for health. KCGH was set up in 2020 to ensure that the value of GH knowledge gained abroad is recognised and applied in the Netherlands. KCGH focuses on facilitating knowledge transfer to benefit the Dutch health system. To date, we have mainly tapped into the knowledge of GH&TM medical doctors and supported the activities of several NVTG working groups, but we aim to work with the broader health sector, for example the municipal health services (GGD).

KNOWLEDGE EXCHANGE STIMULATES NEW PERSPECTIVES

At KCGH, we seek to stimulate thinking beyond one's own opinions and frame of reference. The brain is sparked by taking new perspectives, leading to surprising discoveries and insights. While there are other GH knowledge actors in the Netherlands, KCGH's enabling role sets us apart.

We facilitate the process of knowledge transfer by:

- connecting GH experts and knowledge users;
- stimulating health professionals to share GH knowledge and experiences with others;
- offering thinking space for health professionals to assess the utility and application of GH knowledge in the Netherlands.

Specifically, KCGH organises online and in-person meetings and events, including symposia, dialogues, workshops and webinars. We also award an annual prize for a thesis and dissertation directly connected to our mission. This year's winner will be announced in December.

ENABLING YOU TO MAKE YOUR EXPERIENCE USEFUL

Are you a student or health professional with an idea or insight to share? We welcome input from all health professionals, not just GH&TM medical doctors. Your current – or relevant past – working experience in health settings in low- and middle-income countries (LMICs) could well be useful for the Dutch context. We will help you capture it, transform it into actionable knowledge, and transfer it to Dutch health professionals. We can provide communications and organisational advice, connect you to our broad network, and may even offer some financial support.

KCGH: facilitating GH knowledge transfer to the Netherlands
KCGH enables the exchange of GH knowledge in the Netherlands. As facilitators, we do not fund research or training abroad. Instead, we connect GH experts to each other and to Dutch knowledge users. KCGH also supports the process of applying the knowledge to the Dutch health system. As an additional benefit, we stimulate a more global perspective on health. KCGH was set up by the Netherlands Society for Tropical Medicine and International Health (NVTG) and the Training Institute for International Health and Tropical Medicine (OIGT). It is subsidised by the Dutch Ministry of Health, Welfare and Sport (VWS).

Which Global Health insights for the Netherlands would you like to share? We look forward to hearing from you.

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nvtg verenigt global health professionals

Membership of the Netherlands Society for Tropical Medicine and International Health (NVTG) runs from 1 January to 31 December and may commence at any time. Membership will be renewed automatically unless cancelled in writing before 1 December. Membership includes MT*b* and International Health Alerts. An optional subscription to TM&IH carries an additional cost. Non NVTG members can subscribe to MT*b* through a student membership of the Society for € 40 per year by sending the registration form via our website www.nvtg.org/lidworden or by sending name and postal address by e-mail to: info@nvtg.org
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