

Tissue nematodes

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Trichinella sp

Summary

- Trichinellosis = Trichinosis
- *Trichinella*: adult worm in intestinal wall (not in the lumen), larvae in muscles and heart
- Transmission by eating infected meat, so there is never a free-living parasite
- Hypereosinophilia, fever, muscle pain, oedema chiefly peri-orbital
- Faeces negative for parasites (no eggs)
- Muscle biopsy positive for larvae
- Filaria are part of tissue nematodes

Historical note

In 1835 a 51-year-old Italian bricklayer died of tuberculosis in St Bartholomew's Hospital, London. Jim Paget, a first-year student (later of "Paget's disease" or osteitis deformans fame), was present during the autopsy and observed fine hard white inclusions in the diaphragm. Similar inclusions had been observed by doctors from time to time in the past but were attributed to commonplace muscle calcification, which quickly blunted the dissecting scalpel. Paget inspected the lesions with a hand lens and with a compound microscope in the British Museum. At the time there was only one such instrument in the entire Museum and it belonged to Robert Brown, of "Brownian motion" fame. Paget quickly recognised their worm-like structure and wrote of his discovery to his brother. After the word got out, surgeon Thomas Wormald took a second piece of the "sandy" diaphragm to Richard Owen, at that time assistant conservator of the Hunarian collection in the museum of the Royal College of Surgeons. He later became a major figure in

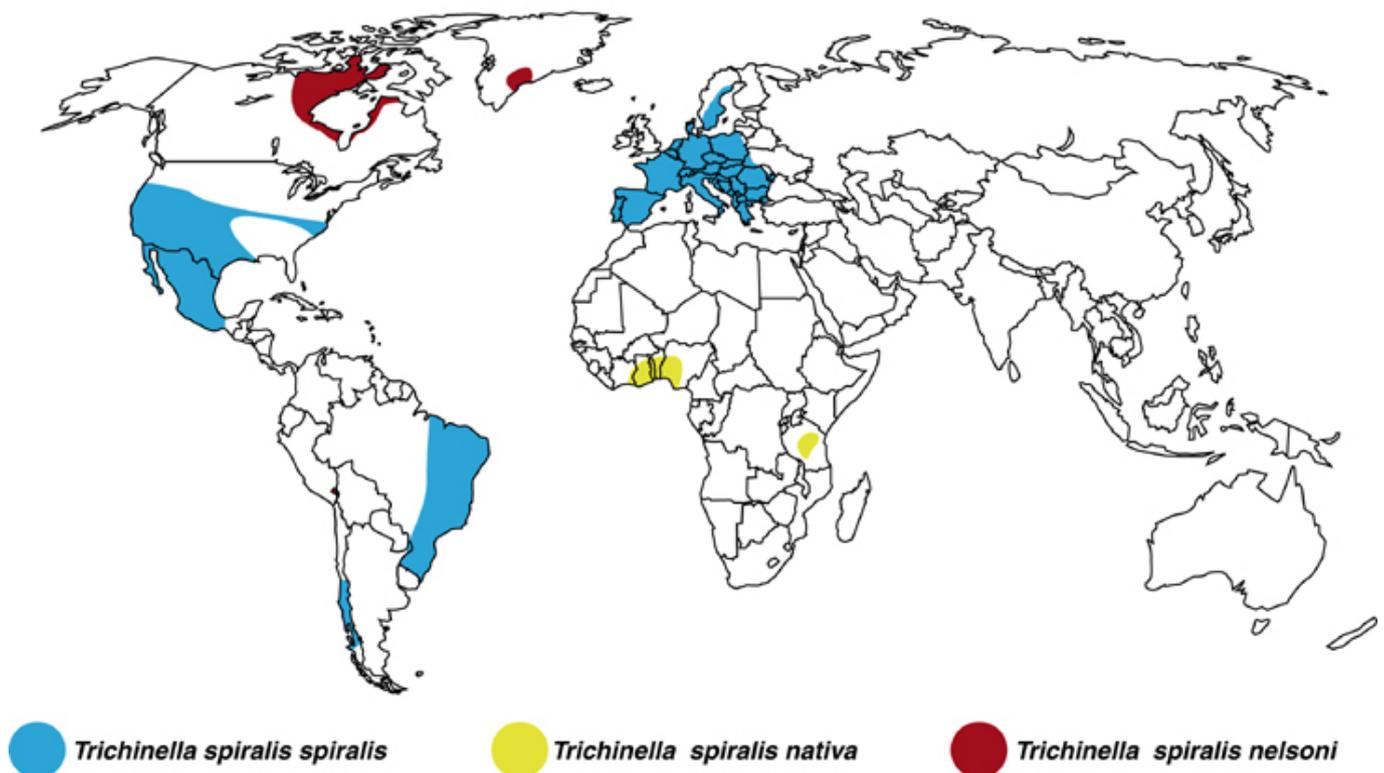
comparative anatomy and paleontology, coining for example the name “Dinosauria”. He published the discovery of the parasite (“a microscopic entozoon”, but didn’t give the proper credit to Jim Paget. The name “*Trichina spiralis*” was suggested. This name *Trichina* had already been given to a fly, and the name was later changed to “*Trichinella*”. In 1846, the American Joseph Leidy found *Trichinella* larvae in the pork he had for dinner. He hypothesized that trichinosis is caused by consuming undercooked pork. In 1859 Rudolph Virchow carried out transmission experiments in which infected human muscle was fed to a healthy dog. After only 3 to 4 days adult *Trichinella* worms were found in the dog’s duodenum and jejunum. He also discovered that heating the meat for 10 minutes was enough to stop transmission. He started to spread the message that eating raw or lightly smoke-cured ham was dangerous. In Germany, where sausages were an important part of the daily diet, he provoked resistance from the German Veterinarian’s Society. At a public meeting when denounced by a veterinarian, he showed the public an infected piece of ham and challenged his opponent to dare to eat it. In front of the crowd the veterinarian wisely declined the offer. Virchow’s reputation grew quickly after this incident. When later challenged to a duel by Baron von Bismarck, he choose infected sausages as his weapon. The Baron declined to eat them after hearing what trichinosis was but the two men became friends later on. These days, Virchow is mainly remembered as the father of cell theory (“*omnis cellula e cellula*” or every living cell comes from another living cell).

PS. Robert Brown died in 1858, just before Charles Darwin received news from Alfred Russel Wallace’s independent discovery of the role of natural selection in the evolution of animals and plants. It was Brown’s death that provided the vacant slot in the Linnean Society’s programme that allowed Darwin (spurred on by Wallace’s findings) to describe his theory (and Wallace’s) in public.

General

Geographical distribution of *Trichinella spiralis*

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Map showing the areas endemic for the different subspecies of *Trichinella spiralis*: *Trichinella spiralis spiralis*, *Trichinella spiralis nativa*, *Trichinella spiralis nelsoni*. Copyright ITM

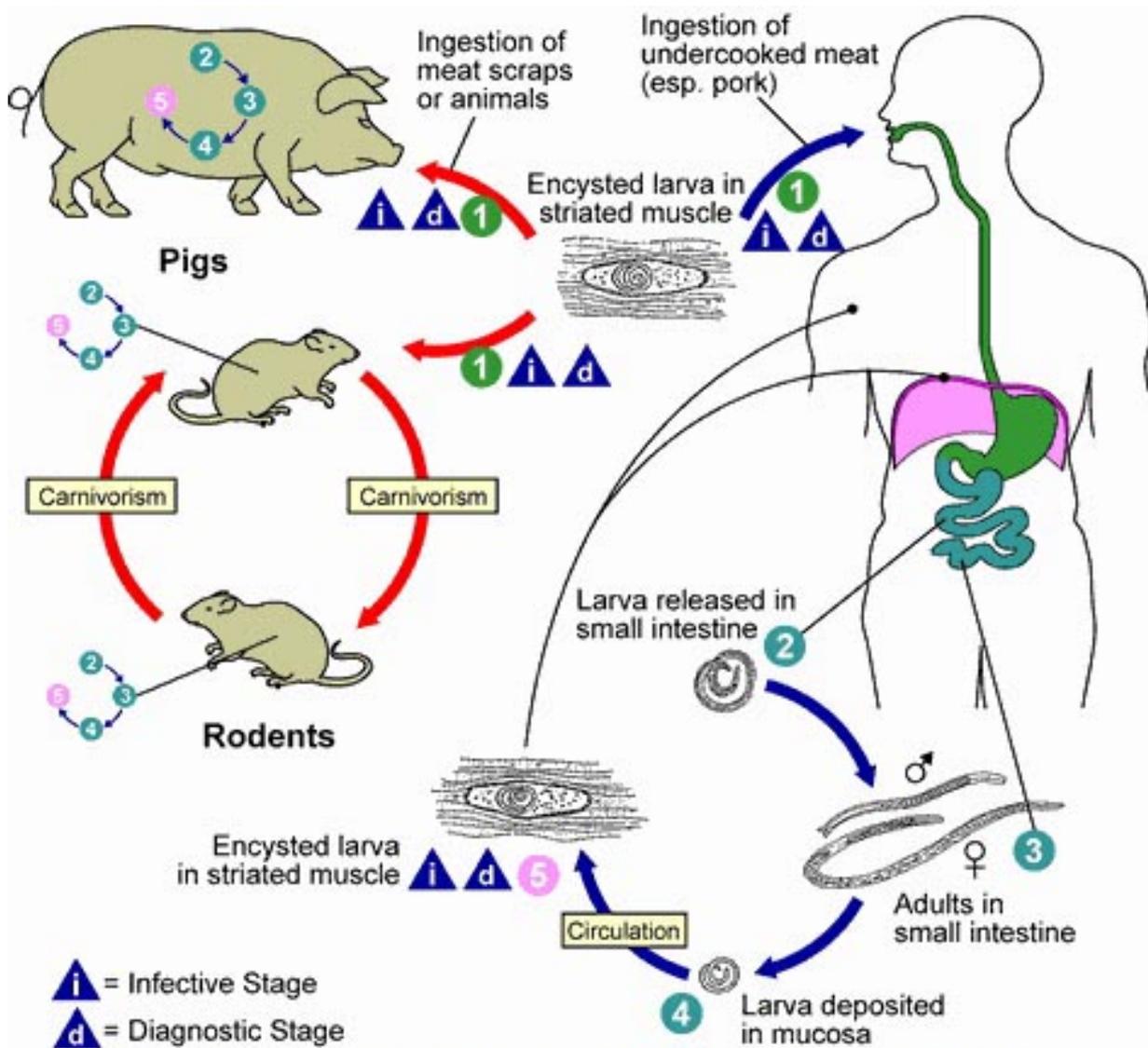
Trichinosis or trichinellosis is a zoonosis. It refers to infection with the larval and adult stages of a group of closely related nematodes which belong to the genus *Trichinella*. The infection is meat-borne.

Typically pork is implicated. Other meat sources such as horses and wild game, certain birds and even reptiles increase in significance as more study results are becoming available. Carnivores and omnivores represent the most important reservoirs.

Trichinella species

There are 9 *Trichinella* species. All species can develop in mammals and some in birds or

even reptiles. The parasites are widespread on all continents except Antarctica. *T. spiralis* occurs in temperate regions and infects mainly pigs. *T. nativa* occurs in the arctic and subarctic areas in terrestrial and marine carnivores (e.g. polar bear, walrus). These parasites are resistant to freezing which is important for meat storage. *T. britovi* occurs in temperate areas of the Palearctic region, as well as North and West Africa. *T. spiralis nelsoni* occurs in Africa and southern Europe with a reservoir in wild carnivores and wild pigs.



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Trichinella spiralis life cycle. Courtesy of CDC, Division of Parasitic Diseases

More than 100 species of mammals are susceptible to the infection. By and large pigs and horses seem to be responsible for the majority of human infections. Horses are considered herbivores, but 32% of horses tested ate meat when offered. The feeding of animal products to horses is a practice that occurs in several countries. Eating walrus meat plays a role in the arctic. On a global scale *T. spiralis* is responsible for the majority of human infections. Rats play an important part in the transmission in pig-raising areas. It is unclear if they form a true reservoir. The use of rat pesticides can actually augment transmission as poisoned rats are easy prey for pigs.

Gravid female worms embedded in the intestinal mucosa release newborn larvae. These larvae measure about 100 μm by 6 μm . These immature larvae are extracellularly exposed to the humoral immune system. The larvae migrate to the intestinal lymphatics, then enter blood vessels and subsequently penetrate striated muscle cells. Then something strange happens. After entering the muscle cell, the larvae are completely intracellular. This is unique. They will convert their host cell into a so-called nurse cell. Their metabolism is mainly anaerobic, which helps their survival after the death of the host. In the muscle cells, larvae can survive several decades. They are now called infective larvae and are visible with low magnification. Larvae do not mature or become encapsulated in heart muscle. When a new host ingests muscle tissues, the larvae are released in the stomach by digestion. In the duodenum they penetrate the villi and undergo 4 molts, developing into adults which measure about 1 mm (males) to 3 mm (females) with a thickness of about 30 μm . Males and females copulate and 6 to 7 days post-infection, the females start to produce new-born larvae. This continues for a few weeks according to the immune response of the host. Afterwards adults are expelled. It is extremely rare to find an adult worms in a human patient.

Clinical aspects

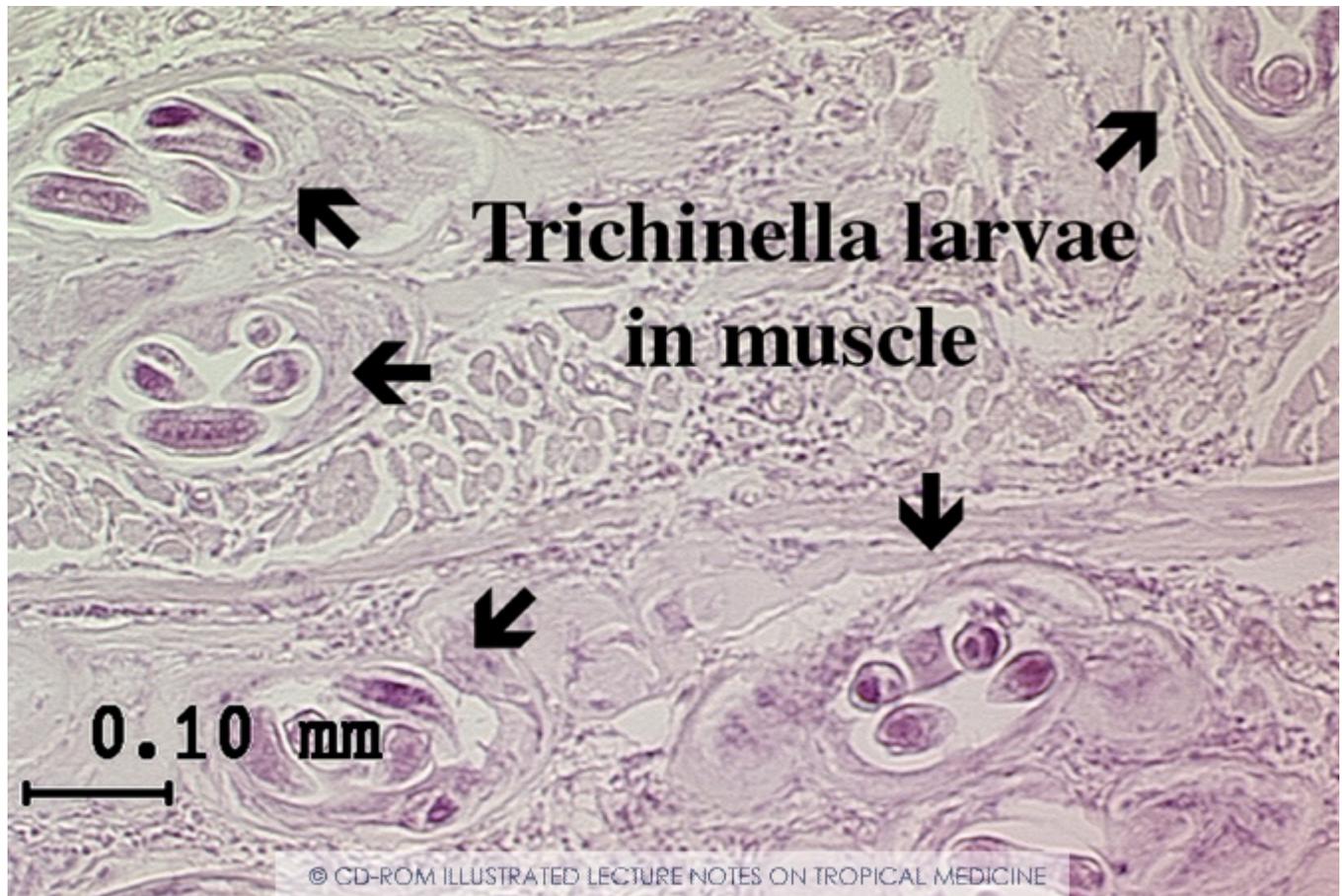
Light infections may be asymptomatic. About 70 live larvae are sufficient to provoke clinical disease. In more typical cases there is nausea, non-bloody diarrhoea, abdominal pain, vomiting and fever; a few days after eating infected meat. After 10 days the fever tends to increase. The patient is very ill, asthenic and debilitated, there are muscle pains and a typical peri-orbital oedema (differential diagnosis acute trypanosomiasis, angioedema, gnathostomiasis and nephrotic syndrome). This oedema is caused by invasion of the small

muscles around the eye. In severe cases, oedema extends to arms and legs. Conjunctival and subungual haemorrhages may occur (due to vasculitis, not endocarditis). There may be signs of myocarditis, encephalitis, urticaria and asthma. A small number of persons may develop a maculopapular rash after the onset on muscular pain. There is often very significant eosinophilia. This lasts from several weeks to three months.

A massive decrease in eosinophils in persons with severe trichinellosis predicts a severe outcome. Myositis causes an increase in the muscle enzymes (creatine phosphokinase, CK). Wandering newborn larvae can become trapped in small blood vessels leading to vasculitis and peri-vasculitis with diffuse or focal lesions in the central nervous system. Aspecific cortical and subcortical lesions (ischemia) can be identified on MRI, and much more rarely, white matter lesions (granulomatous reaction). Severe myalgia generally lasts for two to three weeks.

Dyspnoea is relatively common and is primarily caused by invasion and inflammation of the diaphragm. After a few months the symptoms are reduced or disappear, although asthenia and chronic muscle pain can persist for up to 6 months. Mild infections are self-limiting but live larvae will persist in muscles for years.

Diagnosis



Trichinella spiralis in a muscle biopsy. Copyright ITM

The clinical picture is of a patient with acute fever and myalgia, pronounced asthenia, possibly diarrhoea and a swollen face. Cardiopulmonary, neurological or renal complications may be fatal. The consumption of insufficiently cooked or raw meat can often be found in the patient's history, and this is often game that the patient has hunted (e.g. wild boar) or raw meat eaten in Asian cuisine or the Arctic.

Here it is important to consider the incubation period; one week for severe disease, two weeks for moderate disease, and three to four weeks for benign forms. Sometimes the infection can be traced to infected horsemeat. There is leukocytosis with eosinophilia, although eosinophilia can be absent in immunocompromised persons (renal graft, HIV, chronic myeloid leukaemia). Muscle biopsy should be performed (deltoid muscle or other). An

infection is clinically patent in humans when the number of larvae per gram of muscle biopsy is around ten and severe when above hundred. In early stages of infection, histology is more sensitive than trichinelloscopy. The larvae can be seen coiled inside myocytes. There are various serological techniques (e.g. ELISA, Western blotting) for identifying antibodies against *Trichinella* species. Serology is negative during the first days of the febrile phase (seroconversion during second to fifth week of infection). PCR can be performed in the International *Trichinella* Reference Centre (Istituto Superiore di Sanita, Rome, Italy). Remember that there will be no eggs in the faeces.

Treatment

For mild infection symptomatic treatment is often sufficient. In the early stage albendazole (800 mg/day) or mebendazole at high doses can eradicate adult worms in the intestine. Mebendazole is poorly absorbed. Albendazole 800 mg daily for 7-14 days may be used, in combination with high-dose prednisolone. With treatment the duration of the disease may be reduced to one or two weeks. Pyrantel is sometimes used during pregnancy, but its efficacy is disputed.

Prevention

- Meat should be well boiled or roasted through.
- Importance of meat inspection. The identification of *Trichinella* larvae in muscle samples is limited to post-mortem inspection of carcasses. Selection of muscles for sampling in meat inspection requires identification of predilection sites in a particular animal, but in low grade infection, distribution of the larvae is not homogeneous. In pigs infected with *T. spiralis*, predilection sites are the diaphragm crus, the tongue and the masseter. The diaphragm of a slaughtered animal is inspected (the piece of muscle of a certain minimum weight is flattened between two glass slides and examined using transillumination). This technique (trichinoscopy) is not so good for *Trichinella pseudospiralis* because it is not surrounded by a capsule and is easily missed. Pooled muscle samples can be inspected with a method which employs artificial enzymatic digestion to free and to look for the larvae.
- Pig food (which may include infected rats) should be boiled for 30 minutes.
- To store pork for 10 days at -25°C is generally impractical in developing countries. In the

West meat is sometimes irradiated with high doses of gamma rays, which will kill any larvae.

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Angiostrongylus cantonensis

Life cycle and transmission

In 1938, *Angiostrongylus cantonensis* was discovered in rat lungs by Chen in Canton, China. The first human case description dates from 1945. Recently, the taxonomical position of the worm as changed and *A. cantonensis* has been transferred to the genus *Parastrongylus*, but in this text we will continue to use the generic name *Angiostrongylus*. Infection with *A. cantonensis* is the most common aetiology of eosinophilic meningitis. Angiostrongyliasis occurs primarily in Southeast Asia, throughout the Pacific Basin, including Hawaii, Fiji, Indonesia, Philippines, Japan, mainland China, Taiwan and Papua New Guinea, but also in several Caribbean nations (Bahamas, Cuba, Puerto Rico, Dominican Republic and Jamaica). Occasionally small outbreaks occur.

Final hosts

A wide variety of rodents are final hosts, primarily in the genera *Rattus* and *Bandicota*. Eggs laid by the female worm hatch in branches of the pulmonary arteries. After hatching, first-stage larvae enter the alveoli, migrate up the trachea, are swallowed and reach the alimentary tract. Subsequently, they are excreted in the faeces of the animal. When a snail consumes these droppings, infection of the mollusk will ensue. Within about two weeks, infective third-stage larva will appear. When ingested by a rodent, these L3 larvae migrate to the brain via the blood circulation and develop into fourth-stage larvae and then young adults within the next 4 weeks. They migrate to the subarachnoid space, enter the venous plexus, and are carried to their final destination, the pulmonary arteries.

Humans and rats become infected through eating raw slugs or snails, soiled lettuce contaminated with mollusks, eating a carrier (“paratenic”) host, such as infected planarians,

land crabs or freshwater shrimps. Certain freshwater as well as marine fish can become infected. Inside man, the neurotropic third-stage larvae pass from the intestinal tract to the meninges. They die 1-2 weeks after arriving in the human brain. Adult worms do not occur in humans.

Clinical aspects

Angiostrongyliasis (infection with *A. cantonensis*, the rat lungworm) has an incubation period of 2-35 days. Symptoms are due to migration of the larvae in the brain and the inflammatory reaction which occurs. The disease presents with acute moderate to severe headache (100%). Besides the headache, patients can complain of eyeball pain. Visual problems can occur, due to involvement of one or more cranial nerves (diplopia, acute strabismus, gaze palsy) or due to migration of the larva into the eye, which can lead to retinal detachment and blindness. Nuchal rigidity occurs in about 66% of patients and Brudzinski's sign is present in \pm 66%. Facial nerve paralysis, transient ataxia, delirium, seizures, cognitive dysfunction, hyperesthesia in various dermatomes and paraesthesia of arms and legs, trunk or face may occur and some symptoms may persist for months, although chronic disease is rare.

Vomiting and nausea are self-limited and stop after a few days. Fever occurs in less than 50% of patients. The disease tends to be more serious in children. The disease is self-limiting. Most symptoms disappear spontaneously within 4 weeks of onset (range 2-8 weeks). Mortality is less than 1%.

Diagnosis

Eosinophilia of peripheral blood or CSF is not always present on initial laboratory testing. Pleocytosis may be absent early in the course of infection. Larvae are rarely detected in the CSF. The CSF can be clear or cloudy, but does not contain blood (except in case of a traumatic tap). The absence of focal lesions on CT or MRI-scanning of the brain distinguishes *A. cantonensis* infections from most other helminthic infections of the brain. Immunodiagnosis (ELISA, Western Blot) is possible in some centers.

There is a poor correlation between the serological results of serum and CSF. Since in most cases, larvae will not be recovered in the cerebrospinal fluid and an autopsy will not be

performed (the infection is not lethal in general), the diagnosis will be a tentative one, relying on the history, positive serology and exclusion of other causes.

Treatment

Analgesics are usually needed. Steroids (e.g. prednisolone 60 mg/day x 2 weeks or dexamethasone) shorten the duration of the headache. When performing a spinal tap, the opening pressure is increased in about 60% of patients. Repeated spinal taps to reduce the intracranial pressure are sometimes performed. Antihelminthics are thought by some not to be effective and considered to worsen the symptoms, probably because of the inflammatory reaction to antigens released by dying worms. Some clinicians use mebendazole or albendazole, but controlled studies are lacking.

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Gnathostoma sp.

Nematodes of the genus *Gnathostoma* belong to the *Gnathostomatidae*. At least 13 species have been identified, with 5 recorded in humans. Various species may cause severe infections in humans: *G. spinigerum* (in several geographical areas), *G. doloresi*, *G. hispidum*, *G. nipponicum* (all 3 only in Japan), *G. binucleatum* (only in the Americas). Humans are infected by eating raw or undercooked shellfish, freshwater fish, frogs or chicken. The male worms are 10-25 mm long and the females' measure 25-55 mm. The third-stage larvae, which are responsible for disease in humans, measure about 3 mm. The final host for *G. hispidum* is the pig. The usual final hosts for *G. spinigerum* are dogs and cats. The eggs reach the outside world in the faeces. If they are dropped into water they will hatch 10 days later.

Freshwater copepods (*Cyclops*, belonging to water fleas) are the first intermediate hosts. Fish, amphibians and various mammals may become infected by eating the infected *Cyclops*. There is low host-specificity and humans can also become infected.

The incubation time can be as long as 10 years. The larvae cannot develop into adult worms in humans. They migrate through the body and in doing so may trigger itching, transient

subcutaneous swelling with local erythema and possible discrete pain. These symptoms occur after an interval of days to weeks. The swellings are caused by local oedema, necrosis and haemorrhages within the migration path. If the larvae penetrate vital organs (e.g. the brain) the situation may become life-threatening.

Gnathostomiasis is an important cause of eosinophilic meningitis and myelitis. Almost all cases of neurognathostomiasis are reported from Thailand and result from infection with *G. spinigerum*. Gnathostoma larvae typically enter the spinal cord along the nerve roots resulting in radiculomyelitis.

The worm can ascend the spinal cord and reach the brain. This journey can take several years. Spinal cord disease result in radicular pain followed by ascending paralysis of legs or quadriparesis with bladder dysfunction and eosinophilic pleocytosis in the cerebrospinal fluid. Diagnosis can be confirmed via serology. Most often ELISA is performed, followed by Western Blot if positive; a positive 24-kD band is nearly 100% specific for gnathostomiasis. Mechanical / surgical extraction of the larva is possible in a minority of patients (11% in one series).

No randomized trials of antihelminthic therapy have been conducted. The treatment is symptomatic and if possible / necessary also surgical. Albendazole 400 – 800 mg daily for 21 days is often used as an etiologic treatment. An alternative is two repeated doses of ivermectine. Corticosteroids have been used to treat cerebral and spinal oedema.

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Toxocara sp.

Nematodes of the genus *Toxocara* belong to the Ascarididae. *Toxocara canis* and *T. cati* are parasites which can cause a **visceral larva migrans** syndrome (fever, hepatitis, pneumonitis, urticarial, eosinophilia) with or without asthma. If they reach the retina, they may lead to **chorioretinitis** with blindness as a possible outcome. Infection occurs by swallowing an egg that has reached the outside world via the feces of a dog (*T. canis*) or a cat (*T. cati*). A *Toxocara* parasite may become adult and eggs may appear in the faeces of

humans in exceptional circumstances (e.g. HIV infection AIDS).

Definitive diagnosis is established via detection of larvae in a tissue biopsy, though symptoms rarely justify such an aggressive diagnostic approach. ELISA is useful for visceral larva migrans, but not for ocular larva migrans. Cross-reactivity with other parasite antigens is common. Treatment is based on steroids and albendazole or diethylcarbamazepine (DEC). Nevertheless the effect of the anthelmintic treatment on the extra-intestinal larvae is limited. Intra-ocular infection resulting from *Toxocara* larvae may lead to traction upon the retina resulting in retinal detachment. Vitreoretinal surgery has a good chance of leading to an improvement in vision in approximately 50% of cases.

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Filariasis

Summary

Major filariasis

Lymphatic: *Wuchereria* (90%) and *Brugia* (10%)

- Lymphangitis + adenitis + superinfection
- Lymphatic obstruction with hydrocele, lymphoedema and elephantiasis
- Chyluria, intermittent fever and asthmatic syndrome.
- Microfilariae principally at night in blood
- Transmission via mosquitoes

Onchocerciasis: *Onchocerca volvulus*

- Skin nodules, pruritus, eye lesions, swollen lymph nodes, sometimes lymphoedema
- Microfilariae in skin samples (snip, scarification) and eye (anterior chamber)
- Transmission via simuliids

Loiasis: *Loa loa*

- Calabar oedema, subconjunctival migration across the eye, subcutaneous migration
- Microfilariae in blood during the day
- Transmission via fly which bites during daylight

“Minor” filariasis

- Mansonellosis (*M. perstans*, *streptocerca*, *ozzardi*)
- Dirofilariasis (*D. immitis*,...)
- Dracunculiasis (*D. medinensis*)

Filariae are nematodes that live as adults in various human tissues. They do not lay eggs, but constantly produce enormous numbers of larvae (microfilariae) in humans. These are found in the skin or blood.

Human-to-human transmission occurs via insects: the parasites are thus “arthropod-borne”. Animal reservoirs play no role of significance in most places, except in subperiodic *Brugia malayi*. Filariasis only exist in warm climates because of the high temperature necessary for the development of the worm in the vector.

There are several species of filariae, but 6 are commonly pathogenic:

- *Wuchereria bancrofti*
- *Brugia malayi*
- *Brugia timori*
- *Loa loa*
- *Onchocerca volvulus*
- (*Mansonella streptocerca*)

There are 2 filariae that are often well tolerated by humans: *Mansonella perstans* and *Mansonella ozzardi*.

The reason for this tolerance is not known; however it should be recognised that not all

people infected with these filariae are asymptomatic. Insufficient is known about these parasites.

Dirofilariasis is for the most part only of anecdotal importance and no microfilariae are found in humans.

Dracunculiasis is traditionally included among the filariasis, although there are marked clinical differences between this parasite and the other filariae.

Lymphatic filariasis

General

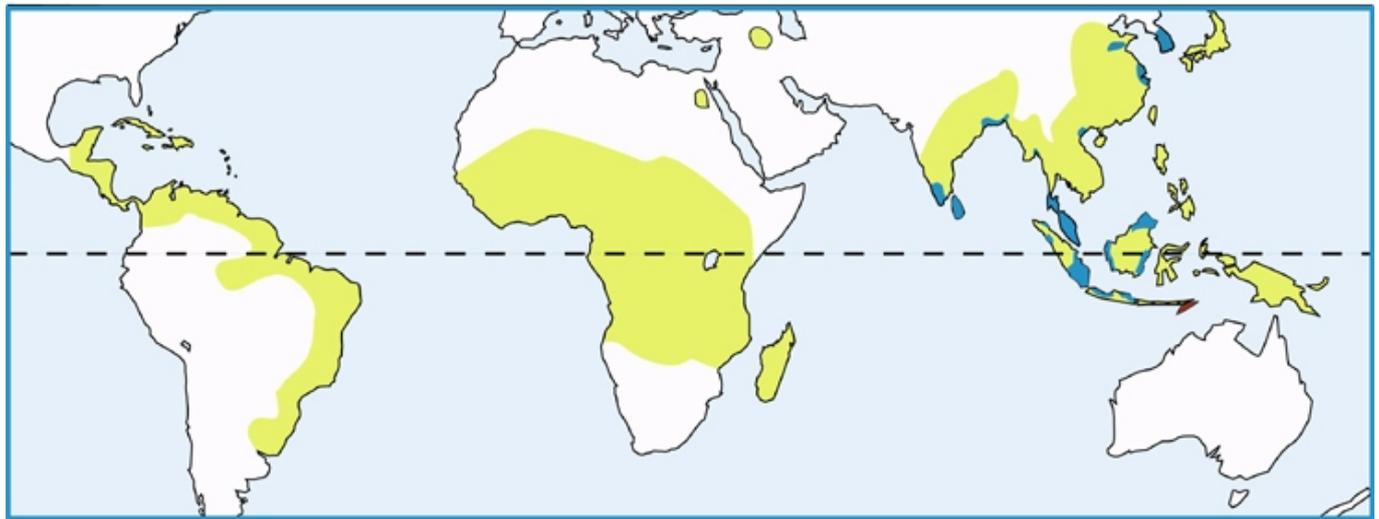
Wuchereria bancrofti, *Brugia malayi* and *Brugia timori* cause lymphatic disorders. *Wuchereria bancrofti* is the most widespread of the human filariae in the world. The majority of infections occur in Asia, but this parasite also causes considerable problems in Africa and the north-west of South America. There is a periodic and a subperiodic form.

B. malayi occurs in Southeast Asia. There are two forms: a periodically transmitted form (without animal reservoir) and a subperiodic form (animal reservoir in monkeys). Consequently, subperiodic *B. malayi* infection is a zoonosis.

Brugia timori is limited to a few islands around Timor.

Parasite	Rhythm	Reservoir	Main vector
<i>W. bancrofti</i>	Periodic	Humans	Culex, Anopheles
<i>W. bancrofti</i>	Subperiodic	Humans	Aedes
<i>B. malayi</i>	Periodic	Humans	Anopheles
<i>B. malayi</i>	Subperiodic	Humans, monkeys, cats	Mansonia
<i>B. timori</i>	Periodic	Humans	Anopheles

Lymphatic filariasis
map of distribution



 *Wuchereria bancrofti*
 *Brugia malayi*
 *Brugia timori*

Lymphatic filariasis, geographical distribution

Transmission

It became clear that the parasites are transmitted via the bite of infected mosquitoes, primarily by the night-biting *Culex (quinquefasciatus)* and *Anopheles* mosquitoes. This biting behaviour is important as the numbers of microfilariae in the peripheral blood systematically fluctuate over a 24-hour period reaching their highest levels at night. There is a remarkable periodicity of the microfilariae. The density of parasites is greatest at the time when the chance of transmission is greatest (at night).

Wuchereria bancrofti becomes adult in human lymphatics and lymph nodes. The adult female worms are 0.2 mm wide and can be up to 10 cm long. The males are shorter (40 x 0,1 mm). *Brugia* adults are about half this size. They can survive for up to 20 years, but the average life time is 5 years. Approximately 8 months after infection *W. bancrofti* microfilariae appear in the circulation. For *Brugia* sp, this prepatent period is about 3 months.

Historical note

In 1866, the German doctor Otto Wucherer discovered numerous microfilariae in patients with haematuria and chyluria in Bahia, Brazil. In 1872 the Briton, Lewis, in Calcutta discovered that patients with elephantiasis were infected with filariae. Bancroft was the first to discover the adult worm in an abscess and later in fluid which he tapped from a hydrocele during his surgical practice. He was one of the first to suggest that disease was transmitted by mosquitoes, although it was Patrick Manson (1844-1922) who reported the development of filarial embryos in the mosquito. Because microfilariae were periodically detectable in the blood, the Scottish doctor Patrick Manson suspected that night-biting mosquitoes might be responsible for transmission.

Pathogenesis

The adult worm induces an immunological reaction in humans. The basic lesion is a sterile inflammation around the worm; in and around the lymph nodes and lymph vessels. In the case of lymphangitis, there is often retrograde inflammation (centrifugal spread). This inflammation leads to obstruction of lymph vessels, resulting in temporary lymphostasis and lymphoedema. Following repeated attacks, irreversible damage to the lymphatics occurs with permanent “non-pitting” lymphoedema. Sometimes abscesses occur at the site of dead adult worms. There is also evidence that indicates adult worms can themselves directly attack the lymphatics (irrespective of the immunological response).

In humans with severe symptoms, low or no microfilaraemia is often found, whereas humans with high microfilaraemia often have no symptoms. The reasons for this apparent paradox is, that the resulting pathology is caused by the patient’s own immunological response to the adult worms. If the reaction is violent, few adult worms and microfilariae survive but considerable inflammation will occur with sequelae. During infection with the filariae the immunological response evolves. Down-regulation can occur and some patients do not produce any interferon-gamma after exposure to parasitic antigen.

This is currently the subject of intense study. It is likely that this influence on the immune system explains the many asymptomatic patients in endemic areas. Both infected amicrofilaemic and microfilaraemic patients display lymphangiectasis on ultrasound or

scintigraphy. The adult worms seem to induce multiplication of endothelial cells and dilatation of lymph vessels, even in the absence of inflammation. On the opposite side, when there is a violent immune reaction against the microfilariae, Weingarten syndrome appears (see below).

Worm load

There is no multiplication of adult parasites in humans so that the worm load and the degree of illness is proportional to the number of infective larvae transmitted by infected insects. The number of insect bites is directly proportional to the duration and intensity of exposure in a filariasis region. In most cases; severe disease is only seen in humans who have lived for a long time in an endemic area. The patient's individual immunological response has a significant role in the development of the various symptoms.

Endosymbiont

The intracellular *Wolbachia* endosymbiont is apparently an obligate parasite of these worms. These bacteria are related to *Rickettsiae*. Their presence appears to be favourable for the growth and fertility of the nematode. This has become a target for therapeutic intervention, after it was observed that *Wolbachia* is susceptible to tetracyclines.

Clinical aspects



Severe myxedema as complication of hyperthyroidism. This needs to be distinguished from lymphatic filariasis

The majority of infected people exhibit no or few obvious clinical signs even though they can have microfilariae in their peripheral blood. Although these people are asymptomatic or paucisymptomatic, almost all have subclinical disease with microscopic haematuria or proteinuria, dilated tortuous lymphatics and, in males, scrotal lymphangiectasia. Among the more obviously symptomatic the acute temporary signs and symptoms caused by inflammation should be distinguished from those resulting from chronic lymph tract obstruction.

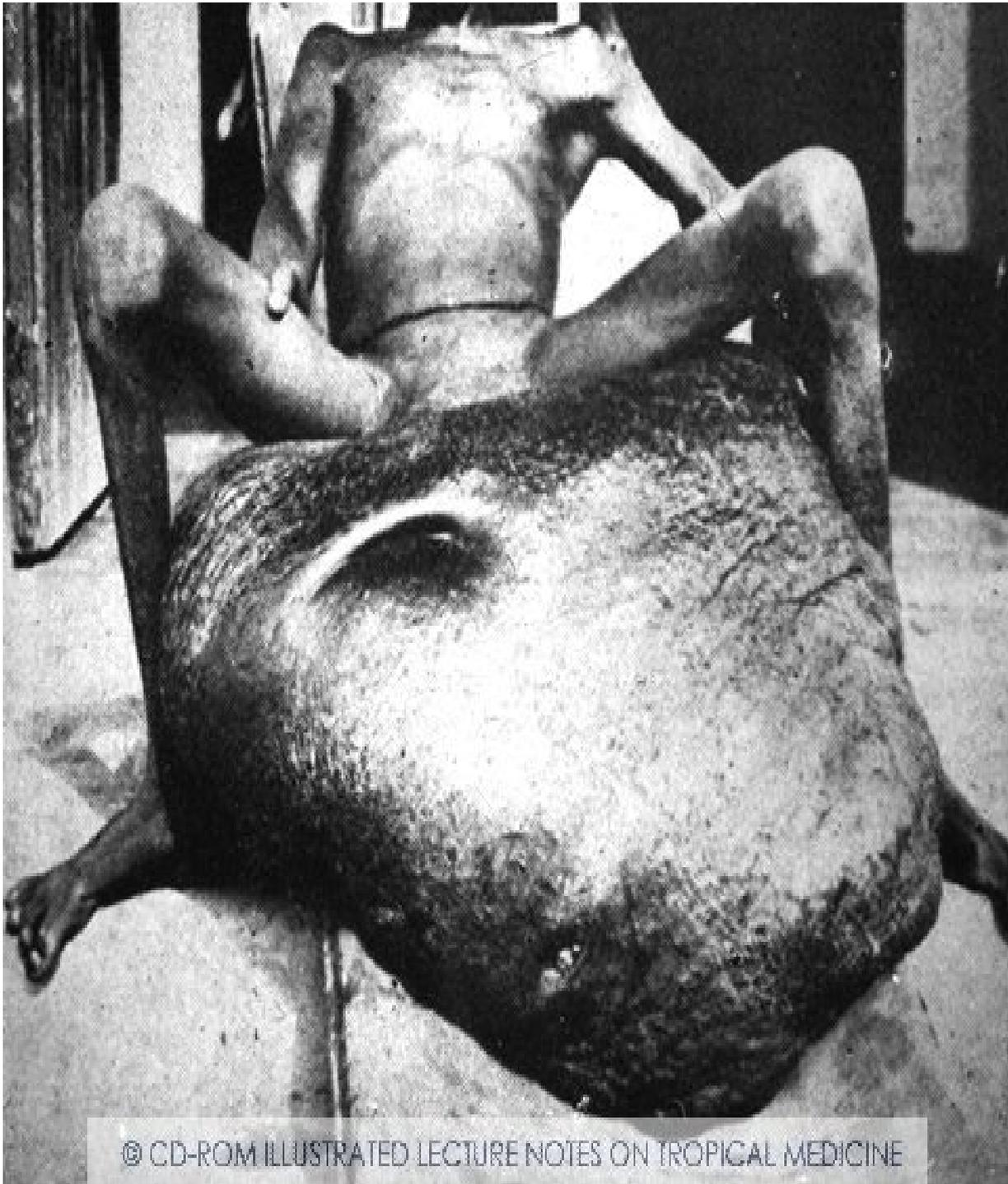
Signs of inflammation

Adenolymphangitis: Acute pain and inflammation in one or more lymph nodes (groin, axilla, elbow, neck). This is associated with fever and general malaise. Retrograde lymphangitis often occurs after 4 to 8 hours. There is centrifugal redness, pain and heat over the course of the lymph vessels. Pyogenic lymphangitis proceeds centripetal, not centrifugal. In most cases, the symptoms last 3-4 days. Each episode results in several days of incapacity for work.

Inflammation of testis and spermatic cord: acute pain, swelling and fever. Repeated funiculitis (inflammation of the spermatic cord) results in thickening of this structure.

Filaria fever: Irregular fever often occurs without external lymph node inflammation, as a result of inflammation of the deeper lymphatics and lymph nodes. The fever may recur irregularly for months or years after the patient leaves an endemic region (observed in 20,000 American military personnel who fought in the South Pacific during the Second World War, an area endemic for *W. bancrofti*).

Signs of chronic obstruction



Wuchereria bancrofti filariasis, elephantiasis of the genitals. Copyright ITM



Wuchereria bancrofti filariasis, elephantiasis of the genitals. Copyright ITM

Hydrocoele: accumulation of fluid in the tunica vaginalis. Hydrocoele often occurs in orchitis (inflammation of the testis). This is very common in endemic regions. Microfilariae are often found in hydrocoele fluid. Large hydrocoeles can be very inconvenient. Sexual incapacity associated with genital filariasis is a major concern for those infected. Shame, anxiety, sexual problems and social stigmatisation are widespread. In the differential, inguinal hernia is important. Besides the fact that it can be reducible or irreducible (even obstructed), it is not possible to feel above the upper edge of the swelling. A testis tumour, tuberculosis of the epididymis and chronic lymphogranuloma venereum and chronic schistosomiasis also need to be ruled out.

Lymphoedema and elephantiasis: Chronic lymphostasis can lead to lymphoedema. The first sign is the loss of contour around the ankles. Later, a reversible pitting oedema appears. After this has turned into non-pitting oedema, the skin will thicken. Lymphoedema is most striking in the legs, scrotum, breasts and arms. The labia and penis are somewhat less frequently affected. If the lymphoedema persists for a long time, elephantiasis can occur. The skin is then markedly thickened and can become wart-like. The oedema is “non-pitting” because there is also a proliferation of connective tissue. The tissue is fibrotic and hard. Recurrent erysipelas (bacterial superinfection) causes the elephantiasis to increase still further. Entry points for bacteria are; fissures caused by athlete’s foot, traditional scarifications, insect bites and small scratch wounds. *Brugia* infections mostly cause elephantiasis confined to lower legs and lower arms.

Lymph leakage: The rupture of swollen lymphatics into the renal pelvis can cause chyluria (milk-like pale pink urine). This can have an insidious or sudden onset. The prevalence is low. It is often recurrent. The chyluria is often more pronounced in the morning and after a heavy fatty meal. This sort of fistula can follow a very chronic course. Rupture of lymphatics in the abdominal cavity or thorax results in chylous ascites and chylothorax (chyle = lymph). A protein-rich white fluid is obtained on aspiration.

Lymph leakage into the area of the tunica vaginalis results in chylocoele. Clumping of lymph proteins in the ureters can cause obstruction. Long-term extensive chyluria results in

hypoproteinaemia. The rupture of numerous small skin lymphatics in the scrotum can lead to a constantly wet, sticky scrotum which is particularly unpleasant.

Tropical pulmonary eosinophilia, Weingarten's syndrome.

Tropical pulmonary eosinophilia is particularly common in India and Southeast Asia. In other geographical areas it seems to be rare. Pulmonary symptoms are predominant: cough, dyspnoea, asthmatic syndrome. Chest X-rays consistently show patchy infiltrates, in contrast to Loeffler's syndrome in which they are more fleeting. Microfilariae can be detected on lung biopsies. Sometimes the lymph nodes swell and splenomegaly occurs. The erythrocyte sedimentation rate increases and there is marked eosinophilia (usually >3000 cells/mm³). There are no microfilariae in the peripheral blood. Serological tests for filariae are strongly positive. This condition responds very well to therapy with DEC (in contrast to Loeffler's syndrome). Usually 6 mg/kg/day x 21 days is given. Steroids can be given if other diagnoses (e.g. strongyloidosis) can be excluded. If not treated it can lead to pulmonary fibrosis. Tropical pulmonary eosinophilia needs to be differentiated from classic asthma, tuberculosis, chronic strongyloidosis, schistosomiasis (does not occur in India), repeated *Ascaris* migrations and toxocarosis.

Endomyocardial fibrosis

Chronic hypereosinophilia can cause cardiac lesions such as endomyocardial fibrosis or fibroplastic endocarditis. The contents of the eosinophilic granules (including major basic protein) are toxic to the endocardium and the adjacent myocardium. A restrictive cardiomyopathy develops.

Clinical difference between *W. bancrofti* and *Brugia* infections.

Brugia infections rarely lead to genital lesions or chyluria. The elephantiasis tends to be limited to below the knee. A filarial dance sign cannot be obtained on ultrasound.

Diagnosis

Microfilariae should be searched for in blood: thin smear, thick smear, concentration method (Knott's test, microfilter). Because of the periodicity, it is best to take the blood at night. A

small dose of DEC can increase microfilaraemia during the day: the microfilariae are then expelled from the pulmonary vascular bed; it is optimal to sample 45 mins after administration of 100 mg of DEC (adult dose). This does not work for people who have a disturbed sleeping pattern. Do not use DEC in an onchocerciasis area (Mazotti reaction). Albendazole and ivermectin do not provoke a release of microfilariae into the peripheral blood. Microfilariae are sometimes detected in chylous urine, hydrocoele fluid and ascites fluid.

Indirect diagnosis can be made by serological detection of antibodies. Serological testing is of limited sensitivity and specificity.

Lymph node biopsies should be avoided as they obstruct lymph drainage still further.

Live adult *Wuchereria* worms can be detected by Doppler ultrasound of the scrotum. Dilated lymphatics are observed in which moving worms are found ("filarial dance sign"). This tool has however limited sensitivity; strangely enough adult *Brugia malayi* are almost never detected by ultrasound.

Circulating antigen of adult *W. bancrofti* can be detected with an antigen-capture ELISA but this is not practical in the field (although it is in a central laboratory). Several ICT tests have been developed which are very simple (like an ICT-test for malaria). There is no diurnal variation in the concentration of free circulating antigen so that nocturnal blood sampling is not necessary. It is a powerful test for studying the efficacy of chemotherapy. People who have no microfilariae in the blood but who do harbour live adult *W. bancrofti* test positive. People who recover no longer have circulating antigen in the blood. For population surveys, the previous standard parasitological techniques (nocturnal blood samples) were cumbersome, time-consuming, expensive and very intrusive. The use of rapid tests detecting circulating antigen has entered the clinical practice in endemic areas.

There is still no commercially available antigen test for detecting *Brugia* infections, which is a problem in *Brugia* endemic regions.

PCR tests have been developed that detect DNA of *W. bancrofti*, *Brugia malayi* and *B. timori*. They are used predominantly in epidemiological work and research settings.

Differential diagnosis lymphedema:

- Primary lymphedema: aplasia or hypoplasia lymphatics, tendency towards symmetrical lesions
- Lepromatous leprosy
- Chlamydia trachomatis, LGV
- Contact dermatitis with recurrent erysipelas
- Pretibial myxedema
- Chromomycosis
- Mycetoma
- Loiasis: Calabar swelling
- Onchocerciasis: hanging groin
- Kaposi sarcoma
- Lymphatic damage (surgery, radiation, burns, TB, malignancy)
- Podoconiosis

Podoconiosis

Podoconiosis (syn. lymphatic siderosilicosis or lymphoconiosis) is a chronic disorder characterised by the very slow onset of oedema, subsequent lymphoedema and later elephantiasis (mostly limited to below the knee). The disease is caused by immunological response to certain minerals (silicates, zirconium or beryllium-containing minerals). When walking barefoot on ground containing these minerals, dust particles can be absorbed through the soles of the feet via small wounds. They are then transported via the lymphatics to the inguinal lymph nodes where they cause a local inflammatory reaction. Atrophy and fibrosis of the lymphatics occur subsequently (in contrast to bancroftiasis where dilatation occurs). The disorder occurs in well-defined areas (specific mineral composition of the soil!) in people who walk about barefoot, such as Ethiopia, Kenya, Rwanda, Uganda, West Africa and India. Whereas lymphatic filariases occur predominantly in lower-lying areas (vector biotope), podoconiosis is characteristic of higher-lying zones. This is not absolute. Other signs of bancroftiasis are absent (hydrocoele, eosinophilia, and nocturnal microfilaraemia). Confusion with mycetoma ("Madura foot") or with classic Kaposi's sarcoma is possible.

Treatment

General

Self-help groups in a community can play an important role. In an acute situation, pain relief, antipyretics and anti-inflammatories are indicated. In chronic lesions of the scrotum, surgery can be performed. Elephantiasis of the limbs is relatively treatment-resistant. Physical methods (lymph drainage by massage) should be continued for a long time and will not in any way alter the fibrotic component of the swelling. Permanent compressive bandages are not practical in a warm, moist environment. A firm, compressive dressing (elastic bandages) may be applied centripetally. These are then changed daily and relatively good results can be achieved in this way, particularly if elastic compressive stockings can be worn afterwards. Microsurgery with the creation of several lymphovenous anastomoses is difficult.

Hygiene and antibiotics

Good, enforced hygiene can dramatically reduce the number of complications. General cleanliness, washing with soap and disinfection of wounds are crucial. If bacterial superinfection is present, this should be treated appropriately. There is often a fungal infection between the toes (athlete's foot), which acts as a portal of entry for various bacteria. Simple hygiene is important and should be stressed:

- Washing the affected part of the body twice daily with soap and water
- Elevation of the affected limb at night
- Keeping nails clean
- Wearing shoes
- Disinfecting skin wounds rapidly and properly
- Systemic antibiotics for superinfection (erysipelas)
- Treating athlete's foot
- Daily physical exercise to improve lymph drainage
- Physiotherapy
- Diethylcarbamazine or DEC

Diethylcarbamazine (= DEC)

Was introduced in 1947. In 1967 Frank Hawking, father of the famous physicist Stephen Hawking, published the results of a study in Brazil of the effect of enriching cooking salt with DEC on lymphatic filariasis. DEC (Notezine®, Hetrazan®, Banocide®) has a **rapid, but indirect microfilaricidal effect** on *Wuchereria* and *Brugia*. DEC somehow modifies the microfilariae so they can be destroyed by the immune cells. If it is taken for prolonged periods, there is also an incomplete macrofilaricidal effect. The dose conventionally given as monotherapy is 72 mg/kg (in total) over 10-14 days (e.g. 50 tablets of 100 mg), although often it will be stated that 3 divided doses after meals will be better. There is evidence to show that lower doses for shorter periods are as effective (e.g. single dose of 6 mg/kg). DEC in monotherapy has an efficacy of $\pm 90\%$ (against microfilariae). Pregnancy is a contraindication for the administration of DEC. This medication is fairly well tolerated, but systemic reactions can occur, caused by the massive and sudden death of microfilariae. Recent studies suggest that these reactions are due to the abrupt release of *Wolbachia* in the human tissues (substantial increase in *Wolbachia* DNA by pCR). Symptoms may include malaise, pruritus, urticaria, fever, headache, vomiting and asthmatic crisis (cf. Mazzotti reaction in onchocerciasis and the Jarish-Herxheimer reaction in spirochaetosis).

This usually happens in the first 48 hours. For mild reactions antihistamines can be used, in severe reactions steroids are indicated. Local tissue reactions can also occur around dead macrofilariae (lymphangitis, abscess, funiculitis). Those local reactions can occur up to several weeks after therapy.

Most microfilaraemic patients have a transient increase of haematuria and/or proteinuria after starting DEC. Because of these potential side effects, treatment is started with a low dose and increased progressively. It sometimes needs to be repeated. The microfilariae are not killed immediately by DEC, but their phagocytosis is facilitated. The indirect effect of DEC means that microfilariae can remain alive in cavities (e.g. hydrocoele). This can give rise to confusion, but otherwise is not important as microfilariae are not pathogenic. If the adult worms are not killed, microfilariae reappear in the blood 3-6 months later.

Ivermectin (Mectizan®, Stromectol®)

This drug became available in 1984 for the treatment of onchocerciasis. It is also active as a microfilaricide against *W. bancrofti*. It has the enormous advantage that it can be given in

one oral dose and has few side effects. It is not macrofilaricidal, even if repeated at high doses. It is useful in the control of bancroftiasis (suppressing microfilaraemia stops transmission to the vectors) but probably not in helping individual patients. The combination of single dose DEC with single dose ivermectin is much more effective (99% of decrease of microfilariae load at least for 12 months) than each medication alone.

Albendazole

Albendazole has a very limited macrofilaricidal effect. It has been shown however that the combination of single doses of ivermectin with albendazole suppresses microfilaraemia by 99% for at least 15 months. This combination is more effective than each medication used separately. This combination also has the great advantage of eliminating diverse intestinal worms and of treating scabies (ivermectin).

Tetracyclines

Tetracyclines are active against the endosymbiotic *Wolbachia*, and their eradication results in long-term sterility and eventual death of macrofilariae. This has become a new therapeutic point of attack, and this is the first effective macrofilaricidal treatment (although indirect and slow). Initial clinical studies showed a favourable effect of a 8-week course of tetracycline on the clinical symptoms and the number of adult worms as reflected by the decrease/suppression of worms detected by ultrasound, decrease/suppression of circulating antigen load. In addition, a much lower rate of adverse reaction was observed when compared to the classic DEC treatment. Subsequent studies showed that a 4-week course of doxycycline has a similar efficacy as a 8-week course, but treatments of shorter duration do not seem to provide the same clinical benefit (although a macrofilaricidal effect was also observed). **Nowadays, a 4 to 6-week course of doxycycline (200 mg/day) is the first-line treatment for the patient diagnosed with acute or chronic lymphatic filariasis.**

Of note, azithromycin does not deplete the *Wolbachia*, so that there is still no therapeutic option for children and pregnant women. A 2 to 4-week course of rifampicin (but not a 1-week course) has substantial anti-*Wolbachia* activity, but its therapeutic implications need to be further studied.

Combination therapy

Combination therapy (albendazole 400 mg + ivermectin 200µg/kg) or (albendazole 400 mg + DEC 6 mg/kg) is largely used in mass drug administration at present to stop transmission. The second regimen is not used in countries where onchocerciasis occurs (risk of Mazotti reaction with acute blindness).

For the individual symptomatic patient, some experts recommend to combine a 6-week course of doxycycline with 14 days DEC, although the clinical superiority of this combination over doxycycline monotherapy has not been demonstrated so far.

Prevention

At the end of the 20th Century, it was estimated that about 120 million people were infected and about 43 million were symptomatic. In May 1997, the WHO adopted a resolution to eliminate lymphatic filariasis as a public health problem. The programme “Global Programme to Eliminate Lymphatic Filariasis” or “Global Lymphatic Filariasis Initiative” was launched in the year 2000. It is based on two approaches:

- annual single dose, two-drug treatment allowing suppression of microfilaraemia for a year and which can be given as mass treatment for 5-6 successive years [albendazole + ivermectin in onchocerciasis areas; albendazole + DEC in other areas],
- simple diagnostic tests that can be performed by a finger prick at any time of the day.

An alternative used in some countries (China, Taiwan) is DEC 0,3% medicated salt x 12 months. It is hoped to eradicate lymphatic filariasis by about 2020. Good financial backing has been provided but this still needs to be extended. Technical training, logistics and management support should be organised. Continuous monitoring and evaluation should constitute an integral part of the programme.

Of note, a recent small study in Papua New Guinea suggests that a triple-drug therapy (DEC + albendazole + ivermectin) would suppress the microfilaremia for up to 2 years (and should be considered in heavily infected patients). This requires confirmation in larger trials.

The focus of disease control has been mass drug administration programs as described above. Vector control with insecticide-treated bed nets is useful where *Anopheles* (night biting mosquito) transmit the parasite. Repellents as personal protection tools prevent on an individual level. Currently, no vaccine exists.

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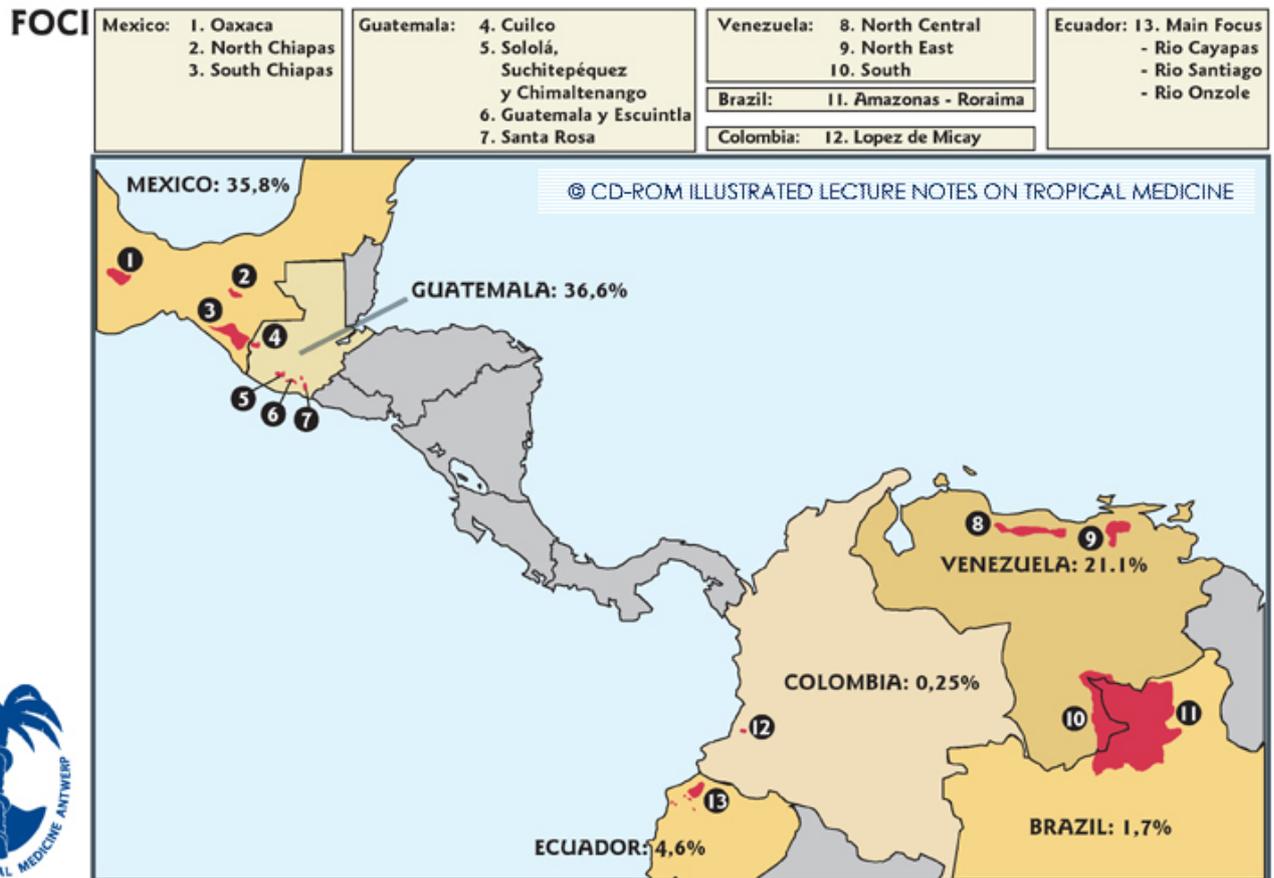
Onchocerciasis

Introduction

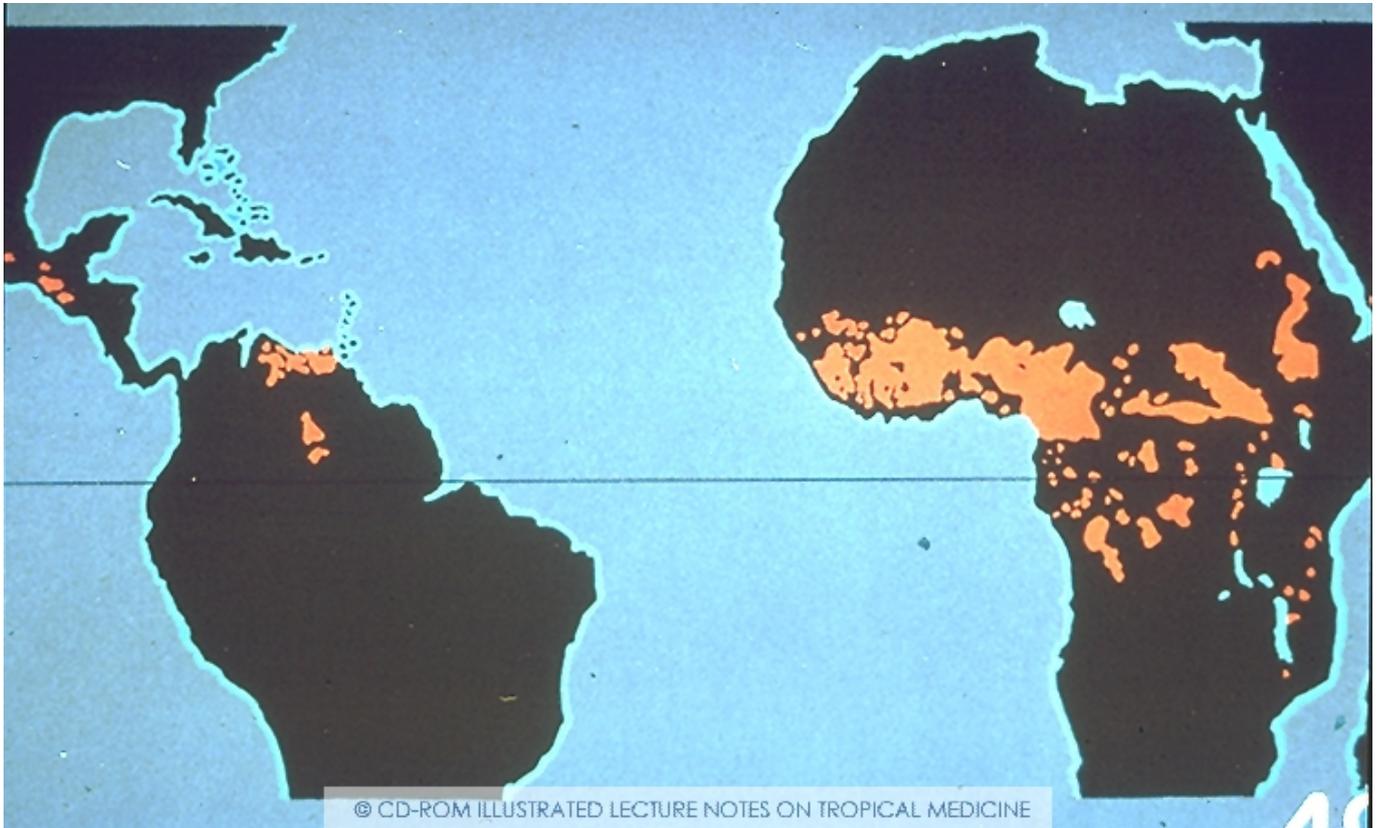
Onchocerciasis (syn. onchocercosis) is a disease resulting from infection by the nematode *Onchocerca volvulus*. The principal characteristics of the condition are pruritic dermatitis, subcutaneous nodules and ocular lesions. It is also known as “river blindness” because the blackfly vector breeds near fast-flowing streams and rivers.

Distribution

ONCHOCERCIASIS IN LATIN AMERICA



Map of onchocerciasis endemic area in Latin America. Adapted from publication of 'Programa para la Eliminación de la Oncocercosis en las Américas - OEPA', with special thanks to Dr Juan Martín Moreira.



Map of endemic onchocerciasis areas.

The disease occurs principally in large parts of Africa, especially West and Central Africa (including both Congos and Angola), but also in Sudan, Ethiopia, the north of Uganda and even Tanzania. About 99% of the cases are now limited to Africa, the remaining being observed in a few foci in Latin America (disease about to be eliminated there).

Vector

The infective larvae are transmitted by *Simulium* mosquitoes (“blackflies”). They reproduce in rocky rivers with fast stream and can cover large distances. The fact that the insects are good fliers makes vector control difficult. Sometimes there are only a few ecologically very suitable places, where thousands of eggs are then laid. This can lead to the sudden simultaneous appearance of massive numbers of adult insects when the environmental conditions are right.

Only female insects suck blood (from humans as well as animals). This happens during the day in the open at well-defined times. The bite is painful.

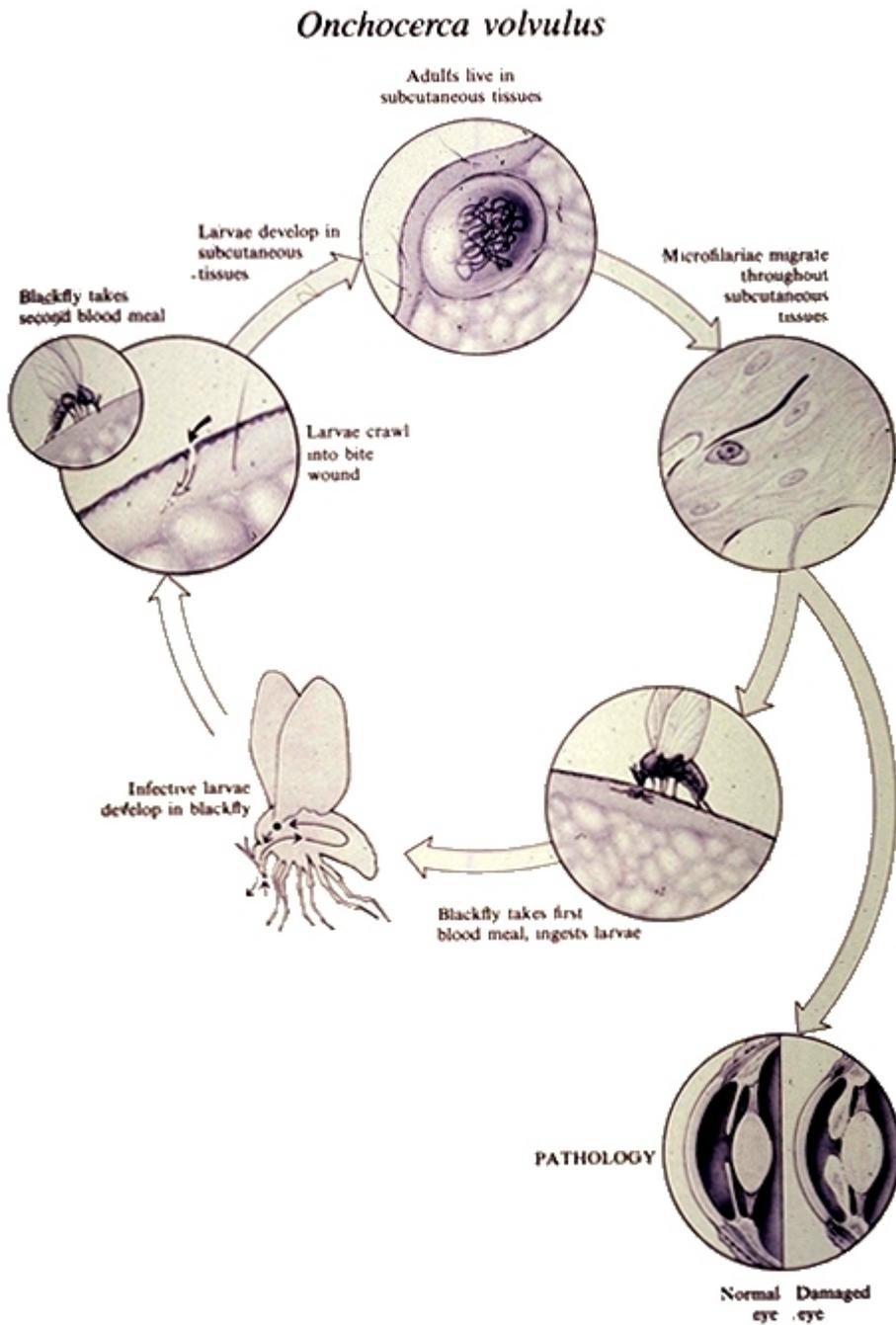
Life cycle

There is no significant animal reservoir. *Onchocerca volvulus* microfilariae are more tissue parasites than blood parasites.

The more insect bites someone suffers over the course of the years, the greater the worm load. After a bite from an infected insect, the infective larvae develop in humans to become adult worms (=macrofilariae) that live subcutaneously. The prepatent period (time between infection and detection of microfilariae) is 3 to 15 months.

The macrofilariae lie coiled subcutaneously in nodules and can live for up to 15 years. These nodules are predominantly located on the scalp and upper body in people living in Central and South America but occur more on the pelvis and legs in Africans. This has to do with the biting habits of the vector.

Simulium damnosum (Africa) tends to bite on the lower half of the body (98% of bites below the belt) and *Simulium ochraceum* (America) preferably bite on the upper part of the body. A female lays on average 1600 microfilariae per day. The microfilariae concentrate in the skin, eyes and lymph nodes. When the microfilariae die they cause a local inflammatory reaction.



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Life cycle of *Onchocerca volvulus*.

Onchocerca volvulus : Endosymbiont

Intracellular bacteria can be detected by electron microscopy in adult *Onchocerca volvulus* and also in the microfilariae. The bacteria belong to the genus *Wolbachia* of the Rickettsiales (Alphaproteobacteria) and are closely related to *Ehrlichia*, *Cowdria* and *Anaplasma*. The *Wolbachia* bacteria are transmitted transovarially, have a preference for oocytes and the lateral tissues (“lateral chords”) in the macrofilariae and have a development cycle that resembles that of the *Chlamydiae*. As for *Wuchereria* and *Brugyia* filariae, they have also become a new point of attack for therapy. It was possible to render the macrofilariae in onchocercomata bacteria-free by means of a 6-week treatment with doxycycline. At the same time parasitic embryogenesis was totally impaired. *Wolbachia* bacteria are also susceptible to rifampicin and this might become an option (like for lymphatic filariasis) for children less than 8 years and pregnant women. How far these findings are relevant for clinical practice has not been fully elucidated. *Wolbachia*-antigen released in the circulation contributes to the discomfort which is seen soon after administration of classic anti-filarial medication, but these symptoms do not seem to occur with tetracyclines.

Clinical aspects

Skin abnormalities

Pruritus occurs locally or systemically. There are scratch lesions often with bacterial superinfection. The chronic itching has given rise to the terms “gale filarienne” and “craw craw”. If untreated the dermatitis assumes the form of a pruritic papular dermatitis, progressing to a chronic rough, coarse, papular dermatitis, often with postinflammatory hyperpigmentation, followed by lichenification, atrophy and finally patchy depigmentation (leopard skin).

Pea- to plum-sized subcutaneous nodules are found predominantly over bony protuberances such as the hip, pelvis, ribs, shoulder blades and skull. These need to be distinguished from cysticerci.

Though not always found (in Africa in only 30 to 60% of positive people), enlargement of the inguinal nodes is sometimes also present, resulting in what is known as “hanging groin”.

Onchocerciasis causes localized elephantiasis (lymphoedema) in a number of cases.

Ocular lesions

Ocular lesions only occur after many years of severe infection and are therefore usually not present before the age of 30. They are more frequent in savanna regions than in the rainforest.

In onchocerciasis patients with heavy infections, microfilariae can be seen in the anterior chamber with a slit lamp. When microfilariae die, opaque fine 0.5 mm wide corneal lesions occur: **keratitis punctate**.

This is corneal inflammation with small spots on the cornea accompanied by redness of the conjunctiva. Sclerosing keratitis occurs later (hazy cornea with pannus formation) as well as iritis and uveitis, resulting in blindness (river blindness!). More rarely, there is involvement of the posterior part of the eye: chorioretinitis and optic nerve atrophy. Ocular lesions can be exacerbated by DEC therapy (**which is therefore formally contra-indicated**) but not by ivermectin.

There seems to exist an epidemiological link between onchocercosis and epilepsy, but more study on this subject is needed to confirm a causal relationship.

The world's leading causes of blindness are:

- cataract (clouding of the lens),
- trachoma (eye infection with the bacterium *Chlamydia trachomatis*),
- glaucoma (increased intra-ocular pressure with damage to the optic nerve),
- xerophthalmia (secondary to vitamin A deficiency with initial night blindness, followed by dry eyes and corneal softening),
- onchocerciasis,
- diabetes,
- leprosy,
- maculopathy and

- trauma.

Diagnosis

Detection of microfilariae in a skin snip

Various techniques may be used for detecting microfilariae in the skin. A skin snip is often used. A needle is used to raise the skin and a fine piece is shaved off with a razor blade. A standardised punch biopsy is also possible. The piece of tissue is placed in physiological saline. The specimen is then examined 15 minutes to 3 hours later to see whether or not microfilariae have emerged. In early infections (first 15 months) not enough microfilaria are present in the skin to be detected with a skin snip.

Detection of microfilariae in skin fluid.

This is done by means of scarification with a sterile razor blade. Preferably several sites are examined (often 4 sites are chosen). The fluid obtained can be collected on a glass slide and stained with Giemsa to allow identification.

Detection of microfilariae at other sites

Occasionally *O. volvulus* microfilariae are found in the blood and in the urine.

Nodulectomy

This is both diagnostic and curative if all the nodules are resected. However the palpable skin nodules are often outnumbered by deeper lying subcutaneous nodules. The macrofilariae are found in the nodule.

Slit lamp examination

This is a non-invasive test, but requires considerable experience. It is best to get the patient

to lay his/her head on his/her knees for at least 2 minutes before the examination to allow more microfilariae to come into the anterior eye chamber.

Mazzotti test

If the diagnosis is doubtful, the patient may be given 50 mg DEC orally. If microfilariae are present, a severe itching reaction will occur within 2 hours. This is caused by an allergic reaction to the proteins released after the rapid breakdown of microfilariae. Because this is very unpleasant, this test should be used only when strictly necessary. An alternative tool, a patch with DEC, is better used (if available) because it causes a localised reaction on the skin.

Serology

Serology cannot distinguish between the various species of filariae. The antigen used is usually extracted from a different worm: *Litosomoides sigmodontis*. It is useless for patient care in endemic settings.

Treatment

Ivermectin (Mectizan®, Stromectol®)

Ivermectin is a fast-acting, safe and effective microfilaricide. Ivermectin has a broad spectrum and is active against various worms and arthropods (ectoparasites). In onchocerciasis, it is active against the free microfilariae and those that are still in the uterus of the female.

It can be given in a single oral dose (4 tablets of 3 mg for an adult; 200 microg./kg in children). It must be given repeatedly. The ideal frequency of administration (once a year or more frequently) still remains to be determined. Ivermectin does not penetrate the aqueous humour. Consequently it does not cause intra-ocular inflammatory reactions that might exacerbate ocular lesions. It was initially thought that pregnancy constituted a contraindication to treatment with ivermectin but no increase in the incidence of abnormalities has been observed in neonates when the product has accidentally been taken by the mothers

during pregnancy. In areas of Loa loa a slight risk of neurological side-effects of ivermectin exists (see below). In 1987 the manufacturer of ivermectin (Merck Company) announced that the company would make the medication freely available to combat onchocerciasis.

Moxidectin

A promising new drug moxidectin, has been shown to have significant macrofilaricidal activity in animal studies and could be capable to interrupt transmission within six annual rounds of treatment. This drug might replace Ivermectin in the future.

Tetracyclines

Tetracyclines such as doxycycline and vibramycin can kill *Wolbachia* endosymbionts of macrofilariae.

According to initial findings, the subsequent suppression of embryogenesis by ivermectin lasts much longer (at least 18 months) and results eventually to the death of the adult worms (macrofilaricidal effect). A four-week course of doxycycline is very effective in killing macrofilariae and is increasingly used in non-endemic settings to avoid repeated annual treatment with ivermectin for many years. In endemic countries however annual administration of ivermectin is still preferred for its fast effect on microfilariae (the pathogenic form in onchocerciasis) and its simplicity of use (mass drug administration of a 4-week doxycycline treatment is unfeasible).

Nodulectomy

This involves the removal of superficial nodules and is (was) popular in Central America.

Prevention

In 1968, the WHO decided to start a large scale onchocerciasis control programme (OCP). The emphasis of the programme is on vector control in areas where the disease is often associated with blindness (savanna-type onchocerciasis). Initially it involved 7 West African

countries (Benin, Burkina Faso, Ivory Coast, Ghana, Mali, Niger and Togo).

After a few years of preparation, the vector control programme started in 1974. In 1978, and subsequently in 1986, the programme was extended to the west and south (including Guinea, Guinea-Bissau, Senegal and Sierra Leone) to a total of 11 countries. It covers an area of 1,235,000 km² with 50,000 km of river. Initially 30,000,000 people lived there. In view of the fact that an adult female worm lives on average 11 years, it was estimated that a minimum of 14 years of insect control would be necessary to eradicate the human reservoir of onchocerciasis. Later, after a successful (but costly) period of intensive vector control, activities focused on regular administration of ivermectin (after 1987 and the free access to this drug) through vertical programs and subsequently primary care settings in order to decrease both morbidity and transmission. At present interruption of transmission has been achieved in large areas and onchocerciasis no longer constitutes a public health problem there.

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Loiasis

Introduction



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Area endemic for *Loa loa* filariasis

Loa loa is a nematode that is solely present in the rainforest area of Central and West Africa. Adult *Loa loa* worms are 3 to 7 cm long and 0.5 mm wide. They live 4 to 17 years. The microfilariae appear 6 to 12 months after infection. They measure 230 to 300 μm by 7 μm .

The microfilariae are found in the blood and exhibit periodicity with the highest density occurring around midday. The adult filaria do not contain a bacterial endosymbiont, as

opposed to *Onchocerca volvulus* and *Wuchereria/Brugyia filaria* where *Wolbachia* is endosymbiotic.

Transmission occurs via the bite of female Chrysops flies. They are insects with beautiful and often yellowish-gold iridescent eyes when they are alive (chrysos = gold). Chrysops flies belong to the Tabanidae, which suck blood of mammals and are active during the day. There is no animal reservoir.

Clinical aspects

The adult worms migrate through the subcutaneous tissues. This migration or the intermittent discharge of large quantities of microfilariae causes transient local oedema: Calabar swellings (Calabar is a place in Nigeria close to the border with Cameroon). There is also local redness and itching. Generalized itching is also described.

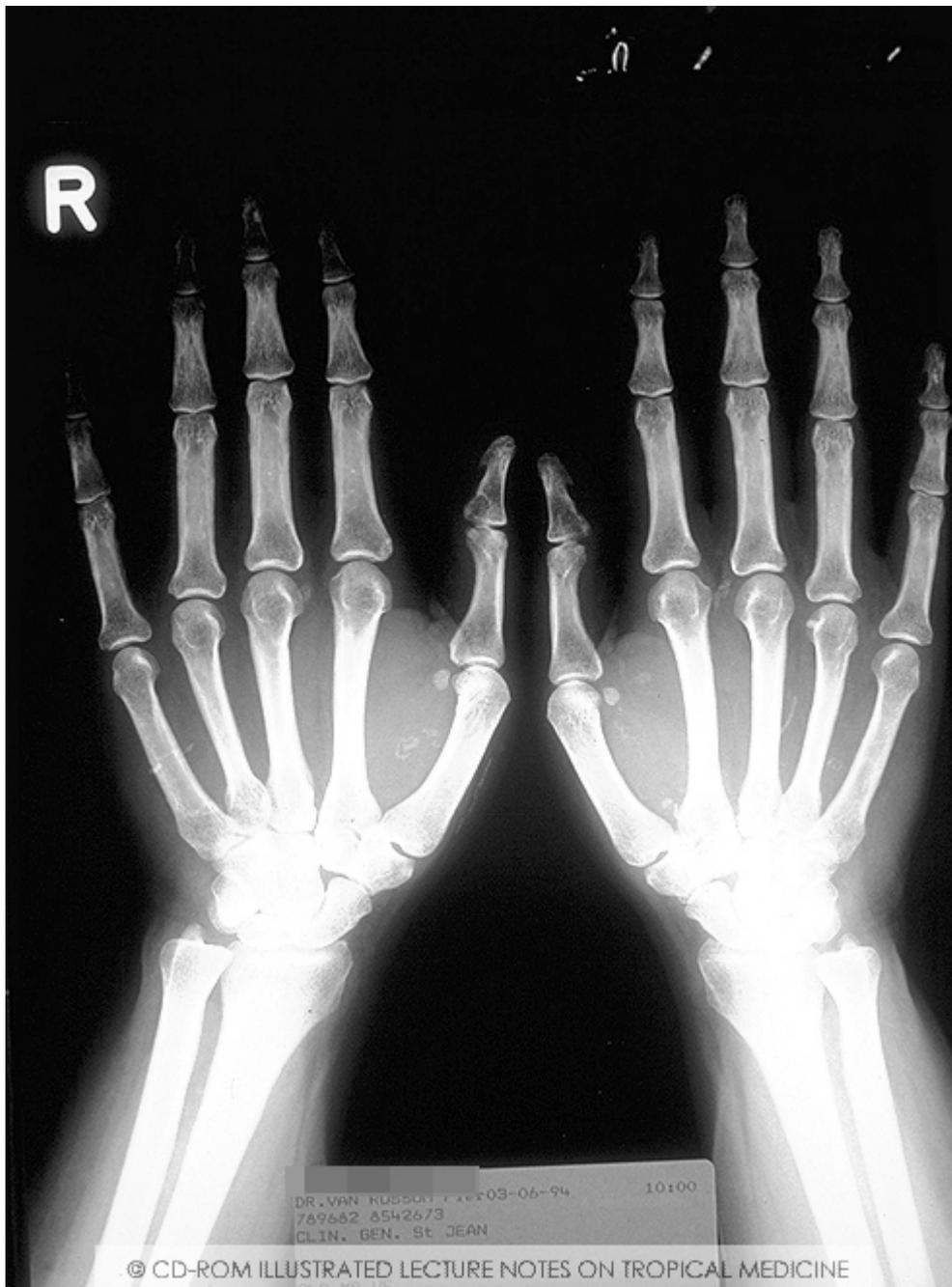
When the worm passes under the conjunctiva, it can be observed and removed (*Loa loa* is for this reason known as the eyeworm). There is no intra-ocular invasion and there is no risk of blindness. The adult worm migrates through the loose-meshed subconjunctival connective tissue. This migration can thus be observed macroscopically, in contrast to the migration of microfilariae of *Onchocerca volvulus*.

The subcutaneous passage of the worms can sometimes be perceived as an itchy and rapidly moving linear swelling. Dead worms can calcify and thus be radiologically visible (e.g. in the hands and wrists). In general, loiasis is accompanied by hypereosinophilia. This increases the risk for endomyocardial fibrosis.

Diagnosis

Serology is aspecific, useless and not performed in endemic areas.

Clinically: Calabar swellings and worm passage across the eye may be considered as pathognomonic for the disease and sufficient to establish a diagnosis in the absence of *Loa loa* microfilariae in the blood.



Dead and calcified adult *Loa loa* filaria, visible on a radiograph of the hands. Copyright ITM

Detection of microfilariae in peripheral blood (during the day) is obtained via a thin blood smear, thick smear or preferably via a concentration technique (Knott or nucleopore filter).

The number of *Loa loa* microfilaria in the peripheral blood can be very high. The higher the number, the higher the risk of neurological complications, especially when drug treatment is started. In order to diminish the risk apheresis can be performed.

Treatment

Treatment of loiasis is based on administration of DEC for 3 weeks. The dose of DEC should be gradually build up over the course of 4 days, up to 400 mg/day. DEC is both micro- and macrofilaricidal against *Loa loa* although often several treatments are sometimes necessary.

Before starting with DEC, simultaneous onchocerciasis should be excluded in view of the risk of extremely unpleasant/severe Mazzotti reactions in the patient.

Ivermectin causes a marked but transient reduction in microfilaraemia. One week after administration on average 10% of the original microfilaraemia still persist.

With high microfilaraemia (>2000/ml; especially if >50,000/ml) there is an increased risk of neurological complications (headache, confusion, gait disorders, hypertension, incontinence, encephalopathy, coma) when DEC is administered. In such cases it is advised to associate prednisone 1 mg/kg for 4 days. Hospitalization for 4 days is advised since most side effects of starting treatment occur in this time frame. In very high microfilaraemia, even the administration of ivermectin (sometimes used to decrease the microfilariae load before DEC treatment) may be risky. In such a situation apheresis may be necessary although it requires complicated and expensive apparatus and specialised personnel (out of reach of most endemic settings). In low-resource settings, a 3-week course of albendazole can be used instead of apheresis in order to reduce microfilaraemias.

Removal of the adult worms during their migration beneath the conjunctiva (local anaesthesia with cocaine or tetracaine) is possible. But if this is not done, the worm creeps on spontaneously and leaves the eye. While extracting the worm from the eye care has to be taken not to rupture the worm, as this leads to a severe inflammatory reaction.

Prevention

DEC 5 mg/kg, 3 days per month can –rarely- be used as prevention in an endemic region. DEC 300 mg per week (dose for adults) is also effective. Vector control is problematical as the breeding sites are very diffuse and widespread and the insects bite out of doors.

“Minor” filariasis

- Mansonellosis (*M. perstans*, *streptocerca*, *ozzardi*)
- Dirofilariasis (*D. immitis*,...)
- Dracunculiasis (*D. medinensis*)

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Mansonella perstans

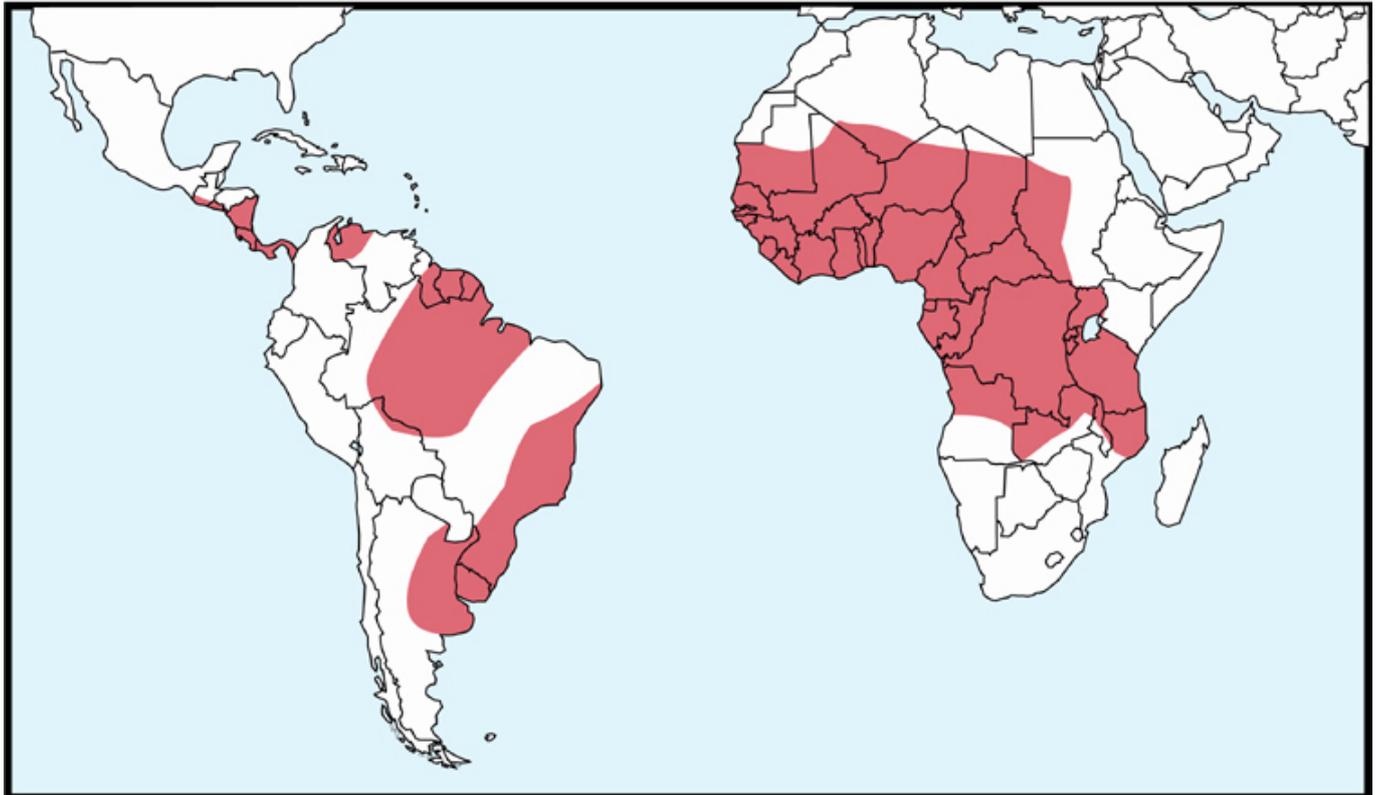
Mansonella perstans (formerly *Dipetalonema perstans*) is a nematode transmitted by *Culicoides* insects. These midges have an aggressive and very annoying biting behaviour principally at dusk but also to a lesser extent at night and during the day. They bite predominantly on hands, arms and head. They often fly in swarms around the face. In view of their large numbers, they can form a very severe plague. Control is difficult.



Midges. *Culicoides* sp. Vectors of *Mansonella filaria*. Copyright ITM

Mansonella perstans

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Map showing areas endemic for *Mansonella perstans* filariasis. Copyright ITM

The infection is widely distributed in Africa but is more localised in Central and South America. *M. perstans* does not occur in Asia.

The adult worms live in body cavities (peritoneum, pleura and pericardium) and in perirenal fat. Most patients infected with *Mansonella perstans* are asymptomatic. A number of different symptoms and allergic reactions are sometimes ascribed to this parasite, but the disease spectrum has not yet been fully established.

The diagnosis is established by detecting the typical small microfilariae in the peripheral blood.

If asymptomatic, no treatment is necessary. A 6-week course of doxycycline with 200 mg/day

resulted in a 97% cure-rate at 12 months in a study in Mali. Ivermectin, albendazole and DEC are inactive.

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Mansonella streptocerca

Mansonella streptocerca



Map showing areas endemic for *Mansonella streptocerca* filariosis. Copyright ITM

Streptocercosis is caused by *Mansonella streptocerca* (formerly *Dipetalonema streptocerca*). This nematode is confined to Central and West Africa. The parasite is transmitted by *Culicoides* midges. It may be a zoonosis as morphologically identical parasites are found in chimpanzees. Adult worms live in the skin. Live worms' cause no lesions but a local inflammatory reaction occurs when they die, with papules and possibly subsequent fibrosis. There are no eye lesions. Differentiation from onchocerciasis is necessary.

Many infected people are asymptomatic. The most frequent symptom is chronic pruritus. The skin is thickened and there are papules. Hypopigmented patches can occur which must be distinguished from leprosy, endemic treponematosis and onchocerciasis. Lymph nodes can be enlarged.

The microfilariae are found in the skin. Detection is as for onchocerciasis (skin snip, scarification with collection of dermal fluid). In the event of doubt or suspicion of leprosy, a biopsy is useful. DEC causes a Mazzotti reaction as in onchocerciasis.

DEC is micro- and macrofilaricidal for *Mansonella streptocerca*. Ivermectin is highly active against this parasite.

Table: Overview of characteristics of microfilariae

Species	Location	Sheath	Period	Length	Tail nucleus
<i>Loa loa</i>	blood	+	Day	275 µm	+ terminal
<i>W. bancrofti</i>	blood	+	Night (periodic strain)	260 µm	-
<i>Brugia malayi</i>	blood	+	Night (periodic strain)	220 µm	+ isolated
<i>Brugia timori</i>	blood	+	Night	290 µm	+ isolated
<i>M. ozzardi</i>	blood	-	-	200 µm	-

<i>M. perstans</i>	blood	-	-	<200 µm	+ double row
<i>M. streptocerca</i>	skin	-	-	210 µm	+ and hook
<i>O. volvulus</i>	skin	-	-	250 µm	-

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Dirofilariasis

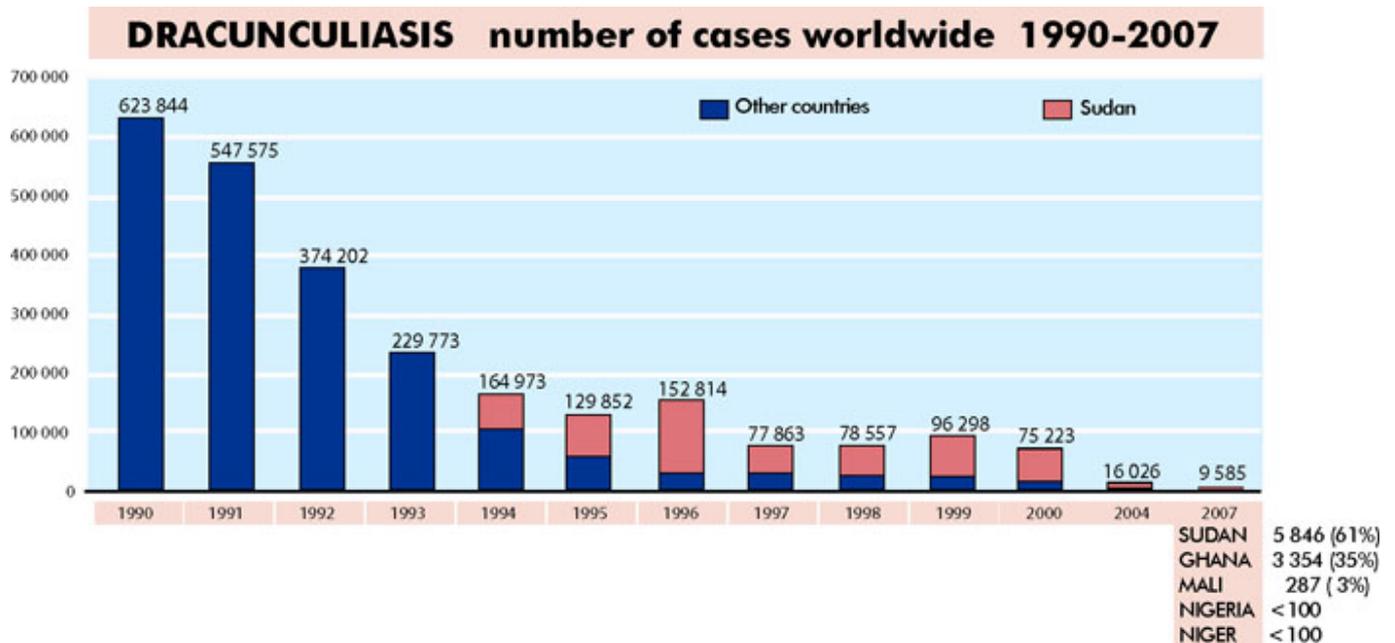
Occasionally humans can be infected by species of filariae which normally have other vertebrates as the final host. The most well-known belong to the genus *Dirofilaria*.

Dirofilaria immitis is a worm that parasitises dogs and cats (so-called heart-worm). The adult worms are 10-30 cm long and are sometimes found in hundreds in the dog's right heart chamber and/or pulmonary artery. The microfilariae are found in the dog's blood and are transmitted via the bite of infected *Aedes* mosquitoes. Man is an accidental host in which further development of the parasite is not possible. Consequently there are no microfilariae in humans. The immature worms die in the branches of the human pulmonary artery which can cause coin lesions in the lung. These are asymptomatic round nodules, 2-3 cm in diameter, which are sometimes found by chance on a chest X-ray (coin lesion). As differential diagnosis with tumour is difficult, the diagnosis is often established on the basis of a lung biopsy. No treatment is necessary.

Other *Dirofilaria* (*Nochtiella*) species (*D. repens*, *D. tenuis*) are sometimes found subcutaneously in a nodule in humans. These nodules can migrate which is clearly different from nodules caused by cysticercosis. *Dirofilaria repens* causes swelling in the subcutaneous tissues in general around the eye, although various other locations are possible including spermatic cord and omentum. Treatment consists of surgical removal. It should be noted that these filariae produce no microfilariae in humans. The diagnosis is usually curative (resection biopsy).

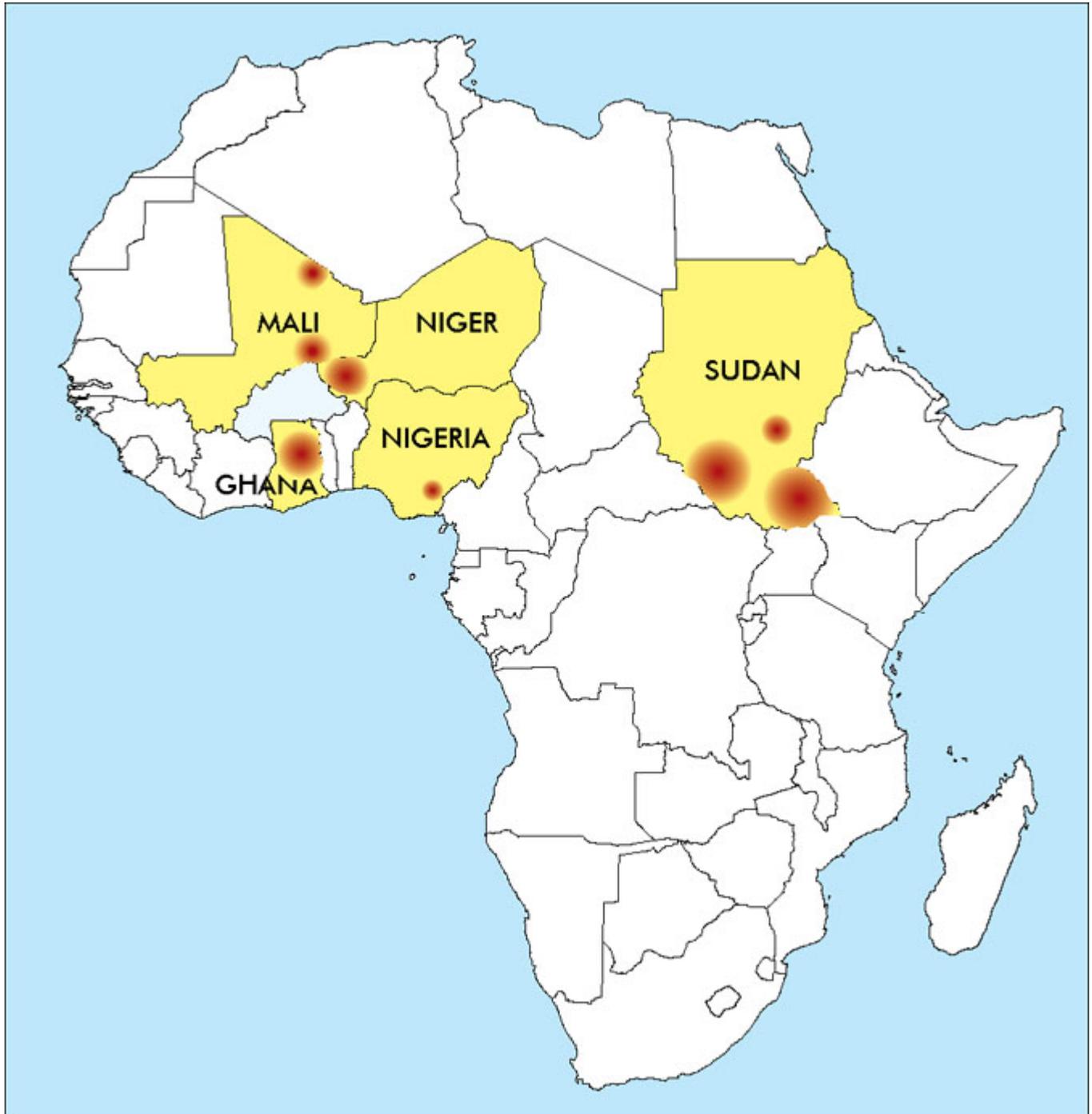
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Dracunculiasis



Graph showing the decrease in number of cases 1990-2007. Copyright ITM

Dracunculus medinensis or Guinea worm, is a nematode that was distributed in the past in several African countries north of the Equator as well as in Central Asia, India and the Arabian Peninsula. During the slave trade cases were introduced into the New World but subsequently the disease disappeared spontaneously. In 1986 the total number of active cases was estimated to be around 3,500,000 and the infection occurred in 20 countries. In 1993 there were 23,735 cases. The last foci in India and Yemen were eradicated in 1996 and 1997, respectively so the disease is now only found in Africa. In 2004, a total of 16,026 cases were reported. Southern Sudan, Northern Ghana and eastern Mali (regions Mopti, Kidal, Gao and Timbuktu) are the three last strongholds of the disease.



Map of the area endemic for Guinea worm.

Year after year, the map changes due to progress in the eradication programme.



Guinea worm



Guinea worm removal



Guinea worm (*Dracunculus medinensis*), life cycle

Humans acquire the infection by drinking fresh water containing infected small water fleas (*Cyclops* sp). After several moults in the water flea, infective larvae are produced. When humans drink water containing infected copepods, the vector is digested in the stomach. The infective larvae penetrate the stomach or the intestine and start maturation in the peritoneum. After 3 months copulation occurs. The male dies and the female grows further to reach her adult length of 60 to 100 cm after approximately 1 year. The long maturation period of approximately one year is required to coincide with the annual peaks in *Cyclops* numbers.

A female worm tends to be localised subcutaneously and causes a painful blister on the skin, usually on the lower legs or feet. The lesion occurs as a result of toxic secretions from the papillae around the parasite's mouth. When the blister bursts it creates an ulcer. When the human host wades in fresh water, the female parasite discharges several hundreds of thousands of larvae. Each time the ulcer comes into contact with water, the female slides out further and releases more larvae a process that repeats itself over a number of weeks until the whole worm is "used up". This process is slow, painful and disabling. The pain is alleviated by contact with cold water. This can be seen as a mechanism for promoting the survival of the parasite as a species because the victim looks for water to relieve the pain. The adult worm dies approximately 3 weeks after its emergence. After its death it will calcify and become visible on an X-ray, for example as an irregular calcified coiled string of about 2 mm diameter which should be distinguished from vascular calcifications.

The best approach is to remove the adult worm in its entirety. The adult worm can be coiled around a stick and one turn made daily. To accelerate expulsion, it is best to keep the wound constantly moist, for example with wet compresses. This however requires approximately 14 days. Surgical removal under local anaesthesia has been described.

Prevention is based on three approaches: safe drinking water, health information (people with wounds should not enter the water) and control of the vector (temephos (Abate®) is an organophosphate harmless to humans but kills the vector *Cyclops*).

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