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A review of neglected tropical diseases: filariasis

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ABSTRACT

Filariasis is result of parasitic infection caused by three specific kinds of round worm. Lymphatic filariasis is found in under developed region of South America, Central Africa, pacific and Caribbian. It has been found for centuries, with main symptoms as elephant like swelling of the arms, legs and genitals. It is estimate that 120 millions peoples in the world have lymphatic filariasis. The spread of diseases and the challenge encountered in its management are discussed along with a review on drugs against filariasis in this article. Detail on clinical effect of drugs on the infection, safety profile, status in clinical practices and drug resistances are also covered.

1. Introduction

Filariasis is a disease caused by parasitic worms called filariae. Filariae are microscopic roundworms that dwell in the blood and tissues of humans. The most important filarial diseases for humans are lymphatic filariases, in which the adult worms are found in the lymphatic system. The lymphatic form of filariasis will be the focus of the site. Lymphatic is also referred to sometimes as "elephantiasis." Elephantiasis is actually an extreme clinical feature of filariasis[1].

2. History of filariasis[2,3]

Due to the fact that there is no reliable written record of lymphatic filariasis before the 16th century, ancient historical evidence of lymphatic filariasis cannot be confirmed. It is known that lymphatic filariasis occured in the Nile region, and ancient artifacts suggest that the disease may have been found as early as 2000BC. A statue of Pharaoh Mentuhotep Ⅱ depicts swollen limbs, a characteristic of elephantiasis, which is a symptom of heavy lymphatic filariasis infection. Artifacts from the Nok civilization in West Africa also show scrotal swelling, another characteristic of elephantiasis. The Nok artifacts date much later than the Egyptian artifacts, from about 500AD. The first written account of lymphatic filariasis comes from the ancient Greek and Roman civilizations. In these civilizations, symptoms of leprosy and lymphatic filariasis are differentiated, and leprosy is described as "elephantiasis graecorum" while lymphatic filariasis as "elephantiasis arabum"[4].

The first reliable documentation of lymphatic filariasis symptoms is from an exploration of Goa between 1588 and 1592[5]. During this trip, Jan Huygen Linschoten wrote that inhabitants were "all born with one of their legs and one foot from the knee downwards as thick as an elephant's leg[4]. More documentations appeared in parts of Africa and Asia soon after. In 1849, William Prout documented a common condition common of lymphatic filariasis called chyluria firstly. This occurs with the passage of lymph in the urine so it appears milky. Such a description is from Prout's book entitled "On the nature and treatment of stomach and renal diseases". In 1863, French surgeon

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Jean-Nicolas Demarquay recorded the observation of microfilariae in fluid extracted from a hydrocoele (another common symptom of lymphatic filariasis) firstly. Three years later, Otto Henry Wucherer discovered microfilariae in urine in Brazil. However, the connection between these two discoveries was not found until Timothy Lewis noted the occurrence of microfilariae in both blood and urine. Lewis also proposed the association between these microfilariae and elephantiasis firstly. Soon after the discovery of microfilariae, the adult worm was discovered by Joseph Bancroft. This species was later named after Bancroft, and was recognized as *Wuchereria Bancroft (W. bancroft)*. Perhaps the most important discovery related to lymphatic filariasis is found by Patrick Manson in 1877. Manson looked for an intermediate host for lymphatic filariasis microfilariae. In 1877, he was finally able to pinpoint the microfilariae in mosquitoes. This discovery was later applied to other tropical diseases such as malaria, and was the first discovery of an arthropod as a vector. However, Manson incorrectly hypothesized that the transmission occurred when the mosquito deposited the filaria in water that then infected humans through ingestion of contaminated water or direct skin penetration. In 1900, George Carmichael Low discovered microfilariae in the proboscis of mosquitoes, and finally pinpointed the true mechanism of transmission, which is attributed to infective bite from a mosquito vector.

As researches on lymphatic filariasis continue, the focuses are on prevalence, treatment, prevention, transmission cycles, and even new species. However, current information on lymphatic filariasis is not complete, and further researches are still needed.

3. Epidemiology of disease

Due to its alarmingly high prevalence in developing countries, lymphatic filariasis remains one of the most important infectious diseases worldwide. Lymphatic filariasis comprises most of the world's filarial infection. One hundred and twenty million people in at least eighty countries are infected with the parasites associated with lymphatic filariasis. 90% of this infection is caused by *W. bancrofti*. Most of the remaining cases are due to *Brugia malayi (B. malayi)*. In addition, one billion people (20% of the world's population) are estimated to be at risk for infection[6, 7].

Although 80 countries are known to be endemic areas, about 70% of infected cases are in India, Nigeria[8], Bangladesh and Indonesia. Lymphatic filariasis is endemic in 32 of the world's 38 least developed countries[9-11].

Usually it takes several months to develope filariasis. People that live or stay in endemic tropical or sub-tropical areas for a long time are at the greatest risk. These regions include central Africa, the Nile delta, Madagascar, Turkey, the Middle East, India, Pakistan, Sri Lanka, Myanmar, Thailand, Malaysia, Vietnam, South Korea, Indonesia, the Philipines, Timor, Southern China, Haiti, Dominican Republic, Guyana, French Guinea, and Costal Brazil. And Short-term tourists are at a very low risk[10,11].

4. Etiology

Filariasis in India is caused by the helminths *W. bancrofti* and *B. malayi*[13]. Macaques and leaf monkeys are reservoirs in some parts of the world. Acute infection is caused by the microfilariae, which are the larval forms and are transmitted by mosquitoes of various species. Chronic filarial lymphoedema is caused by the adult worms which deposit in, and block the lymphatics. Experimental evidence suggests that unless associated inflammation, simple lymphatic occlusion may not cause lymphoedema. Occluded lymph vessels are greatly prone to attacks of lymphangitis followed by edema. Fibrosis block becomes thick and hard with excrescences in the end, which is known as elephantiasis. Lymphoedema and elephantiasis are common in the lower limb, followed by the genitalia[14], the upper extremity, breast and other areas. The commonest manifestation of filariasis is, however, hydrocele. Lymphatic blockage of and around the cysterna chyli may result in retrograde flow and consequent leakage of chyle through the pelvi-calyceal system (chyluria), the intestines (chylous diarrhoea), the skin-generally around the groin (chylorrhagia), the mediastinum (chylothorax), and the peritoneum (chylous ascites)[1,4].

The male: female ratio is 10:1. This may be because women's mode of dress are more covered. About 50% of the patients are in their 3rd or 4th decades of life, though no age is exempt. Most patients are from the lower socioeconomic groups. The incubation period from mosquito bite to clinical manifestation may be as short as 4 weeks but is generally 8-16 months, or even longer. Attacks last 3-15 days and reoccurrence is common.

Asymptomatic infection may occur and may last for life. Acute manifestations of lymphatic filariasis are episodic attacks of lymphadenitis and lymphangitis (fever, pain in the affected part, tender red streaks) along with fever and malaise. Over 90% of cases with chronic manifestations will give a history of acute attacks. Occasionally the adult worms and their associated granulomatous reaction are manifested as lumps in the subcutaneous tissue, breasts or testicles[1, 4, 14].

On the basis of spices of microorganisms, vector etc , it is classified in to four types.

4.1. Lymphatic filariasis

Mosquitoes of the genera *Aedes, Anopheles, Culex,* or *Mansonia* are the intermediate hosts and vectors of lymphatic filariasis[15-17].

Acute lymphatic filariasis is related to larval molting and adult maturation to fifth-stage larvae. Adult worms are found in lymph nodes and lymphatic vessels distal to the

nodes. Females measure 80–100 mm in length and males are 40 mm. The most commonly affected nodes are in the femoral and epitrochlear regions. Abscess formation may occur at the nodes or anywhere along the distal vessel.

Infection with *Brugia timori (B. timori)* appears to result in more abscesses than infection with *B. malayi*[13] or *W. bancrofti*[8]. Cellular invasion, with plasma cells, eosinophils, and macrophages, together with hyperplasia of the lymphatic endothelium, occurs with repeated inflammatory episodes. The consequence is lymphatic damage and chronic leakage of protein-rich lymph in the tissues, thickening and verrucous changes of the skin, and chronic streptococcal and fungal infections, which all contribute to the appearance of elephantiasis. *B. malayi* elephantiasis is more likely to affect the upper and lower limbs, with genital pathology and chyluria being rare.

4.2. Occult filariasis

Occult filariasis referes filarial infection in which microfilariae are not observed in the blood but may be found in other body fluids and/or tissues. The occult syndromes are tropical pulmonary eosinophilia (TPE), *Dirofilaria immitis (D. immitis)* or *Dirofilaria repens* infection, filarial arthritis, filarial breast abscess, and filarial-associated immune-complex glomerulonephritis. TPE most likely results from a hyperresponsiveness to *W. bancrofti* or *B. malayi* antigen. Human infection with *D. immitis* may result in pulmonary lesions of immature *Dirofilaria* worms in the lung periphery. If *D. immitis* larvae lodge in branches of the pulmonary arteries, they can cause pulmonary infarcts.

4.3. Onchocerciasis

Microfilariae from the skin are ingested by the *Simulium* species of blackflies. Chronic onchocerciasis cases are hyporesponsive to parasite antigen with increased eosinophilia, and result in the presence of high levels of serum immunoglobulin E (IgE). Patterns of onchocercal eye disease also are associated with parasite strain differences at the DNA level.

4.4. Loaiasis

Mango flies or deerflies of Chrysops transmit loaiasis. Response to *Loa loa (L. loa)* infection appears to differ between residents and nonresidents in endemic areas. Nonresidents with infection appear to be more prone to symptoms than residents, despite lower levels of microfilaremia. Eosinophil, serum IgE, and antibody levels also are higher in nonresidents with infection[18].

5. Symptoms

Symptoms of lymphatic filariasis can be divided into asymptomatic, chronic, and acute manifestations:

At least half of all patients with lymphatic filariasis appear clinically asymptomatic. This asymptomatic presentation exists despite the presence of microfilariae in their blood and hidden damage to their lymphatics. The length of this asymptomatic period is directly linked to the quality of the patient's immune response[1, 19].

Acute filariasis is characterized by episodic occurrence of inflammation of the lymph glands (lymphadenitis), inflammation of the lymph channels (lymphangitis) and subsequent swelling of the limbs or scrotum (lymphedema). These symptoms are typically accompanied by pulmonary eosinophilia, fever and malaise.

Filariatic fever is often seen with headache and chills, and will usually occur at the same time as lymphangitis.

Lymphadenitis and lymphangitis are characteristic of both the *W. bancrofti* and *B. malayi* forms[8]. In lymphadenitis, the parasite essentially takes over lymph nodes in the body, causing immune reaction and inflammation. Blockage and stretching of the lymph vessels by the adult worms make it difficult for lymph to flow out of the lymphatics and back into the blood stream. Inflammation of the lymph channels and lymph nodes along with a decreased draining efficiency leads to lymphedema.

Lymphatic trunks become very painful and the skin on the arms and legs is covered in red streaks. The distal end of the affected limb becomes swollen during the attack and remains swollen for several days. Usually the swelling is limited to a single limb.

Tropical pulmonary eosinophilia is an extreme immune response to filarial infection. It is characterized by high eosinophilia levels, asthma-like symptoms and restrictive lung disease. This manifestation occurs with low frequency in endemic areas.

In addition to the concurrent exhibition of these symptoms, a patient may suffer from extreme pain in the genital area and may develop filarial abscesses. These pus-filled nodules swell until rupturing when they discharge bacteria and dead adult worms.

6. Pathogenisis

Periodicity refers to the time of day when microfilariae are most prevalent in the blood. This corresponds directly to the feeding habits of the various mosquito species. Most species propagating lymphatic filariasis feed at night with the exception of *Aedes polynesiensis*, a vector of *W. bancrofti*. There is no known natural animal reservoir for lymphatic filariasis. *W. bancrofti* has a curvature of its anterior end and is thinner by comparison to the *Brugian microfilaria*. The microfilaria of *B. malayi* is easily identifiable[20].

During a blood meal, an infected mosquito introduces infective larvae onto the skin of a human host. The larvae then enter the host's body through the bite wound, at which point they migrate to the lymphatics and develop to maturity. This can be a slow process, taking between six and twelve

months. Adult filariae can live for upto 15 years. At the lymphatics, sexual reproduction between male and female adult nematodes results in the production of sheathed eggs known as microfilariae. Female filariae can release microfilariae for up to five years and the microfilariae can live for a year and a half. The microfilariae travel through the lymphatic channels into the blood stream where they are again taken up by the mosquito through a blood meal. Within one to two weeks after uptake by the mosquito, the microfilariae lose their sheath, bore through the stomach wall and enter the mosquitos thoracic cavity where they develop into infective third-stage filariform larvae. The filariform larvae migrate to the mosquito's proboscis from which they are deposited during the mosquito's next blood meal. The larvae penetrate the skin of the vertebrate host and the cycle continues.

7. Diagnosis

The first step towards developing a diagnosis of lymphatic filariasis is to establish a history of exposure in endemic areas. Laboratory tests can follow this basic clinical procedure[2,2-23]. These tests may include:

1) Basic serology testing of peripheral blood for microfilariae detection, keeping the periodicity of the microfilariae in mind[21];

2)A skin biopsy can also be performed, but this test is generally reserved for the infection by tissue-dwelling nematodes (*Onchocerca volvulus*);

3)Recently, ultrasonography using a 7.5 or 10 MHz probe has helped to locate and visualise the movements of living adult filarial worms of *W. bancrofti* in the scrotal lymphatics of asymptomatic males with microfilaraemia[22, 24];

4)New techniques for antigen detection represent the highest quality lab test for diagnosing infection by *W. bancrofti*. PCR tests are of high specificity and sensitivity, and detect parasite DNA in humans as well as vectors in both bancroftian and brugian filariasis[21];

5)Lymphoscintigraphy has shown that even in the early, clinically asymptomatic stage of the disease, there are lymphatic abnormalities in the affected limbs of people harboring microfilaria[19];

6)Immunochromatographic test which are highly sensitive and specific filarial antigen detection assays, are available for the diagnosis of *W. bancrofti* infection[2]. With this test, the parasite antigens can be detected independent of the microfilariae's periodicity. It is rapid (1-10 minutes), and no such test exists for *B. filariasis*.

8. Therapy for lymphatic filariasis

8.1. Drugs for filariasis

Ivermectin and suramin are extremely potent semi synthetic derivatives of the antinematodal principle obtained from *Streptomyces avermitilis*. Nematodes develop tonic paralysis when they are exposed to ivermectin or suramin. It acts aspecial type of glutamate gated CI channel only in invertebrates. Such channels are not involved in the motor control of flukes and tape worms, which are unaffected by ivermectin. Potentiation of GABAergic transmission in the worm has been observed. The lack of GABA related actions in man could be due to its low affinity for mammalian GABA receptors and its exclusion from the brain, probably by p-glyco protein mediated efflux at the blood-brain-barrier. Adult dose of ivermectin is150-200 mcg/kg/d po., and suramin is 66.7 mg/kg/d[25-28].

In 2010 Turner and coworkers proved the microfilaricidal activity of doxycycline against *Onchocerca volvulus(O. volvulus)* in area of *L. loa* co-endemicity[18].

Mebendazole and flubendazole irreversibly blocks the uptake of exogenous glucose by nematodes, leading to glycogen depletion and reduced generation of ATP required for survival. Due to this the parasites die, or are slowly immobilized and cleared from the gut gradually. It does not affect blood glucose levels in humans. Mebendazole is poorly absorbed from the gut, and peak plasma levels are reached in 2 or 4 hours. The drug is excreted in the urine unchanged or as its metabolites. It causes worm death by selectively and irreversibly blocking uptake of glucose and other nutrients in susceptible adult intestine where helminths dwell. Adult dose of mebendazole and flubendazole are 100 mg po. bid for 3 d, second course if patient not cured in three week[3,23,26-28].

Diethylcarbmazine(DEC) has a highly selective effect on the micro filariae. The most important action of DEC appears to be alteration of micro filariae[23], which are readily phagocytosed by tissue fixed monocytes, but not by circulating phagocytes. It also has an effect on the muscular. Activity of the microfilariae and adult worms causing hyperpolarization due to the piperazine moiety so that they are disloged. To decrease risk of adverse effects, low doses (approximately 2-3 mg/kg/d) usually are recommended for the first 3 d of treatment. Higher doses (9 mg/kg/d) are recommended for *L. loa* from days 4-21. Concurrent administration of corticosteroids should be considered with DEC treatment to minimize the allergic manifestations secondary to the disintegration of microfilariae, particularly *O. volvulus* and *L. loa* infections. To avoid adverse effects, doses for the treatment of onchocerciasis and loaiasis start at 50 mg and are increased slowly in frequency and amount[2].

The precise mechanism of action of albendazole is not properly understood. However, it seems to afford its primary anthelmintic effect by binding to the free 3-tubulin present in the parasite cells, thereby causing a more or less selective inhibition of parasite micotubule polymerization, and inhibition of micotubule-dependent glucose-up-take significantly. Besides, the effective inhibition of parasite b-tubulin usually takes place at rather lower strengths of the drug than those that are normally needed to check and suppress human microtube polymerization. Decreases

ATP production in worms, causes energy depletion, immobilization and finally death. Adult dose is 400 mg po.[27,29].

8.2. Surgical treatment

Hydrocele is treated by traditional procedures like excision/eversion. Excision of overlying elephantiasis skin is frequently necessary. Thorough cleaning of the skin is recommended along with peri-operative antibiotic cover as the infection rate is excessive.

Surgery for lymphoedema of the limb can be classified into two main types:drainage procedures and excisional procedures. Drainage procedures are essentially designed to improve lymph flows by either bypassing the block e.g. lympho venous anastomosis or creating additional lymph channels *eg*. omental transposition. Excisional procedures are debulking procedures where the extra large limb volume is trimmed. The procedures differ in the site and type of incision, the way of skin cover and the staging of operations. In Homan's procedure the entire circumference of the leg is cleared in 2-4 stages, while other operations have tried to combine the two.

8.3. Thermal treatment

The Chinese have devised a new method of treatment of lymphoedema by alternatively heating and cooling the leg in an oven. This method is reported to be very effective though cumbersome. Use of a microwave oven has been found to be better.

8.4. Herbal treatments

There are several herbs that have been prescribed by Ayurveda for the treatment of elephantiasis for centuries. The following are some of the herbs reported as having antifilarial activities *ie*. *Vitex negundo* L. (roots)[30], *Butea monosperma* L. (roots and leaves)[30], *Ricinus communis* L.(leaves)[30], *Aegle marmelos* Corr. (leaves)[30], *Canthium mannii* (Rubiaceae)[31], *Boerhaavia diffusa* L.(whole plant)[32].

9. Discussion

True elephantiasis is the result of a parasitic infection caused by three specific kinds of round worms. The long, threadlike worms block the body's lymphatic system-a network of channels, lymph nodes, and organs that help maintain proper fluid levels in the body by draining lymph from tissues into the bloodstream. This blockage causes fluids to collect in the tissues, which can lead to great swelling, called "lymphedema." Limbs can swell so enormously that they resemble an elephant's foreleg in size, texture, and color. This is the severely disfiguring and disabling condition of elephantiasis.

There are a few different causes of elephantiasis, but the agents responsible for most of the elephantiasis in the world are filarial worms: white, slender round worms found in most tropical and subtropical places. They are transmitted by particular kinds (species) of mosquitoes, that is, bloodsucking insects. Infection with these worms is called "lymphatic filariasis" and over a long period of time can cause elephantiasis.

Lymphatic filariasis is a disease of underdeveloped regions found in South America, Central Africa, Asia, the Pacific Islands, and the Caribbean. It is a disease that has been present for centuries, as ancient Persian and Indian writings clearly described elephant-like swellings of the arms, legs, and genitals. It is estimated that 120 million people in the world have lymphatic filariasis. The disease appears to be spreading, in spite of decades of research in this area.

Other terms for elephantiasis are Barbados leg, elephant leg, morbus herculeus, mal de Cayenne, and myelolymphangioma.

Other situations that can lead to elephantiasis are protozoan disease called leishmaniasis, repeated streptococcal infection, the surgical removal of lymph nodes (usually to prevent the spread of cancer) and hereditary birth defect.

If this regime of therapy works, which includes elevation, movement and skin care, it is likely to be of benefit in the management of many other important diseases. This includes management of the skin of patients with AIDS, or for the management of breaks in the surface continuity of epithelium that are highly prevalent in the tropics and in metabolic diseases such as diabetes mellitus or in vulnerable groups such as the bedridden elderly. It requires recognition that the grotesque changes that occur in the most severe cases of lymphoedema are not merely a consequence of lymphatic failure alone. There is in all cases a strong component of both venous and epidermal failure, which responds to therapies specifically targeting at the veins and epidermis.

Conflict of interest statement

We declare that we have no conflict of interest.

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