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## Unraveling the Secrets of Filariasis (Medical Mystery) (From Cure to Elimination)

	
<b>Raghavendra Rao M.V*<sup>1</sup>, Sateesh Babu.A<sup>2</sup>, Sireesha Bala.A<sup>2</sup>, Reshma Fateh<sup>2</sup>, Mahendra Kumar Verma<sup>3</sup>, J.Madhavi<sup>3</sup>, Kumar Ponnusamy<sup>2</sup>, Dilip Mathai<sup>1</sup></b>	
1. Apollo Institute Of Medical Sciences & Research, Telangana state, Hyderabad, India	
2. Avalon University School of Medicine, Curacao, Central America,	
3. Acharya Nagarjuna University, Guntur, AP, India,	
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### ABSTRACT

Early symptoms of filariasis include high fever (Filarial or elephantoid fever). It is an exclusive feature of *W.bancrofti* infection. Repeated inflammatory attacks lead to hyperplasia of the endothelium in addition to cellular infiltration. There is an increase in hydrostatic pressure resulting from the damage to the lymph vessel, which causes an increase in vessel wall permeability. The chronic leakage of fluid contains high levels of protein. The end manifestation of wucherarial infection is Scrotal lymphedema, also known as scrotal elephantiasis, is a "massive enlargement" of the scrotum due to thickening of tissue. Ulceration and secondary infections with bacteria or fungi may occur. Microfilariae usually are not demonstrated in the peripheral blood. Often the "Filarial dance sign" can be seen; which is a characteristic pattern of movement exhibited by adult worms that have been described as rapid and random.



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## INTRODUCTION

Lymphatic filariasis (LF), which is one of the neglected tropical diseases (NTDs) in the world, is caused by *Wuchereria bancrofti* in Africa and transmitted mostly by *Anopheles* and *Culex* mosquitoes(1) Most cases are due to infection by *Wuchereria bancrofti*, which affects patients in equatorial Africa, India, Mediterranean coast, the Caribbean, the eastern and northern coastal areas of South America, and some parts of Central America(2).

The adult worms parasitize the human lymphatic system and cause dilation of lymph vessels. The vessel dilation accompanied by inflammation impairs the normal drainage of lymph fluid and leads to the accumulation of the fluid or lymphedema. The edematous skin is liable to bacterial infections which can trigger an acute febrile symptom or fever attack, and repeated attacks will result in thickening of the skin and eventually disfiguring lesions known as elephantiasis(3).

In the scrotum, dead adult worms may block the lymph vessel and cause accumulation of lymph fluid in the tunica vaginalis, a membranous pouch surrounding the testis. This will produce a swelling of the scrotum or hydrocele (4).

Acute filarial lymphangitis occurs when the adult worm dies, leading to severe localized inflammation. This syndrome appears to be uncommon in untreated individuals (5). The frequency and duration of episodes were recorded for the leg, arm, scrotum, and breast. A very high incidence of acute disease was observed; 0.31 episodes per person-year in the leg alone. Incidence generally increased with age, except in the breast, where episodes were concentrated in the reproductive age range. Males had slightly higher incidence than females in the leg and arm. Chronic disease was strongly associated with acute disease incidence in all locations. Microfilaremia had a statistically significant association with acute disease in the leg, arm, and breast, but not the scrotum (6).

The microfilaria is a miniature adult, and retains the egg membrane as a sheath, and is often considered an advanced embryo. It measures 280  $\mu\text{m}$  long and 25  $\mu\text{m}$  wide. It appears quite structureless *in vivo*, but histological staining makes its primitive gut, nerve ring, and muscles apparent (7) With the introduction of sensitive and specific circulating antigen (CAg) assays, populations living in areas endemic for *Wuchereria bancrofti* infections have been assessed more accurately for both prevalence and intensity of infection(8) Since DEC can cause

anaphylactic reactions pregnant women, children below two years of age and persons who are very sick from other illness are not covered under MDA. When a proportion of the population fails to comply with MDA, a potential reservoir for the parasite is left untreated, opening the door to recrudescence or to potential risk factors for increasing the susceptibility status of newborn and thus reducing the probability of the program's success. It shown that transplacental transfer of circulating filarial antigen (CFA) can lead to in-utero sensitization and immune-modulation in neonates born to filarial infected mother(9,10) The ant filarial drugs currently used, ivermectin in Africa and diethylcarbamazine (DEC) on the other continents, predominantly act against microfilaria in human tissues and to some degree against those in the uterus of the filariae, with DEC showing moderate macrofilaricidal activity against adult worms(11) The classical drugs diethylcarbamazine (DEC), ivermectin (IVM), and albendazole (ALB) have been used for the last two decades as the major mode of intervention for filarial infection in successful mass drug administration (MDA) programmes(12).

The international campaign to eliminate filariasis is now overseen by the Global program to eliminate Lymphatic filariasis, which is coordinated by the WHO. By 2002, national programs were active in 38 of the 80 countries, reaching almost 90 million people. The target was to reach 350 million people by 2005 and 1.1 billion by 2020(13) Current Global Program to Eliminate Lymphatic Filariasis (GPELF) that prohibits pregnant mothers and children below two years of age from coverage targeted interruption of transmission after 5–6 rounds of annual mass drug administration (MDA). However, after more than 10 rounds of MDA in India the target has not been achieved, which poses challenges to the researchers and policymakers. Several studies have shown that *in utero* exposure to maternal filarial infections plays certain role in determining the susceptibility and disease outcome in children (14) As a result of its heritable nature, much more is known about the molecular basis of primary lymphedema (LE) in comparison with what is known about the aetiology and pathophysiology of secondary LE – caused by trauma, environmental factors (e.g. podoconiosis) or infection. The single largest source of secondary LE is lymphatic filariasis (LF), a disease caused by filarial nematodes(15) Second most frequent form of pathology, hydrocele, i.e. accumulation of fluid between the two folia of the tunica vaginalis in the scrotum. In this condition, lymph vessel enlargement and later obliteration, probably including a chronic inflammatory stimulus for the tunica vaginalis to secrete fluid between the two folia, lead to the pathology independent of exogenous bacteria. To quantify

improvement/worsening of hydrocele, a staging system using ultrasonography of the scrotal area has been developed(16) The majority of individuals *born* in endemic areas are chronically infected and many of them are microfilaraemic, without clinical signs of pathology. In long-term studies, the tendency to develop asymptomatic infection with high parasite loads and microfilaraemia was associated with the status of being born from microfilaraemic mothers(17).

Lymph vessel dilation, not obliteration, is probably the early event following antigenic stimulation, which takes place while the adult worms are still alive, i.e. when offspring larvae are being released. Many of these larvae are degenerate and will be taken up by phagocytic cells; it is known that exposure of phagocytes to filarial antigens is accompanied by triggering of the innate immune system(18).

In Ghana, a pilot study was carried out with 39 LF-infected men; 12 were treated with 200 mg doxycycline/day for 4 weeks, 16 were treated with a combination of 200 mg doxycycline/day + 10 mg/kg/day rifampicin for 2 weeks, and 11 patients received a placebo. Patients were monitored for Wolbachia and microfilaria loads, antigenemia, and filarial dance sign (FDS). Both 4-week doxycycline and the 2-week combination treatment reduced Wolbachia load significantly. At 18 months post treatment, four-week doxycycline resulted in 100% adult worm loss, and the 2-week combination treatment resulted in a 50% adult worm loss. In conclusion, this pilot study with a combination of 2-week doxycycline and rifampicin demonstrates moderate macrofilaricidal activity against *W. bancrofti*.(19) The classical drugs diethylcarbamazine (DEC), ivermectin (IVM), and albendazole (ALB) have been used for the last two decades as the major mode of intervention for filarial infection in successful mass drug administration (MDA) programmes However, these drugs are mainly microfilaricidal that is, killing the first larval stage, the microfilariae (Mf). The currently available regimes have been optimised to obtain a decrease in transmission by reducing the Mf load in a given population at both low cost and logistical effort(20).

## **HISTORY**

Filariasis has been known from antiquity. Elephantiasis had been described in India by Sushruta (600) BC and in Persia Rhazes and Avicenna. Clarke in 1709 in Cochin described elephantiasis as "Malabar leg". Ancient Greek scholars differentiated lymphatic filariasis from those of leprosy, describing leprosy as *elephantiasis graecorum* and lymphatic filariasis

as *elephantiasis arabum* (21) However, this is a misnomer, since elephantiasis literally translates to “a disease caused by elephants *W. bancrofti* was named after physician Otto Wucherer and parasitologist Joseph Bancroft, both of whom extensively studied filarial infections. *W. bancrofti* is speculated to have been brought to the New World by the slave trade(22) The adult worm was found in lymphatic abscess by Bancroft in 1882.

Sir Patric Manson experimentally proved that one arthropod vector is responsible for transmitting the disease(23) Microfilaria was first demonstrated in human blood in Calcutta by Lewis(1872)(24)It occurs in all tropical and subtropical countries and it is common in India, South China and the tropical parts of United States, Southern Spain, Europe, Australia. It is also found in West Indies, South America, North America, Sudan, and West Central and East Africa.In India most common along with the coastal areas and in delta areas. Hyper endemic in some parts of Kerala, Tamilnadu, Andhra Pradesh and Orissa(25)The adult worm lives in lymphatic vessels of the human host. A female and male ratio of 4.5 has been reported from surgically removed from adult *W.bancrufti* (26) The life cycle of *W.bancrufti* is of more than usual interest, as Manson's discovery, in 1878, of transmission of this parasite by mosquitoes was the first demonstration of an arthropod as vector of a parasitic organism(27)Among helminthes infections, only filariasis is likely to be encountered in lymph nodes. Lymphatic filariasis affects an estimated 120 million persons worldwide. Among some, the disease is mild asymptomatic, whereas others have a severe, disabling illness related to lymphatic obstruction(28) On September 20, 2007, geneticists published the first draft of the complete genome (genetic content) of *Brugia malayi*, one of the roundworms which cause lymphatic filariasis (29) Determining the content of the genes might lead to the development of new drugs and vaccines(30).

## **SIGNIFICANT GAP IN RESEARCH**

Asymptomatic microfilaremic individuals generally have a marked Th1 hypo responsiveness but a strong Th2 response. In contrast amicrofilaremic individuals with lymphatic pathology have strong Th1 and Th2 responses There is a decrease in gamma interferon(INF gamma)) levels and a significant rise in interleukin-4,production in infected patients, suggesting a profound form of energy. In infected individuals, the levels of IgG and IgE are elevated. The highest levels of IgE were found in microfilaraemic individuals with acute manifestations of filariasis or hydrocele, while highest concentrations of parasitic-specific IgE were found in

amicrofilaraemic individuals. This may suggest a protective effect of IgE, because the highest ratios of specific to total IgE are found in patients with tropical pulmonary eosinophilia (31).

DEC-medicated cooking salt has been used to facilitate mass treatment and has proved to be very effective and safe. DEC fortified salt has been recommended mainly for control programmes chiefly because of its ability to clear microfilaraemias without causing adverse reactions. Program acceleration is required to maximize the number of countries achieving the 2020 elimination targets and minimize the additional efforts required after this year. WHO recently published new guidelines on alternative MDA regimens to eliminate LF (32).

### **WHERE THE RESEARCH GO NEXT?**

*Wuchereria bancrofti* contains rickettsia like Wolbachia endosymbiotic bacteria, which has been suggested to contribute to the inflammatory reactions observed in lymphatic filariasis. Adult *W. bancrofti* can be detected in a high percentage of infected males by ultrasonography of the scrotum. They appear as continuously motile "Dancing worms" that are often clustered in "worm nests" in dilated lymphatic vessels. Worm nets tend to remain in the same locations over time. Adult worms are less commonly visible in lymphatic vessels in the female breast and in the axillary and inguinal regions in male and females. Ultrasonography is useful for assessment of hydroceles and for detecting "Subclinical Hydroceles" that are not detectable by palpitation.

Circulating Filarial antigen (CFA) test detect antigen released by adult *W. bancrofti* worms in human blood, serum, or plasma samples. Commercially available antigen tests include a rapid format card test and an ELISA. Both of these tests are sensitive and specific for *W. bancrofti* infection and more sensitive than tests that detect microfilariae. The card test is widely used in filariasis elimination programs for mapping endemicity and for monitoring progress. Blood CFA levels are related to the number of adult filarial worms in the host. Anti filarial antibody tests that detect IgG4 subclass antibodies to recombinant filarial antigens are more specific for filariasis than earlier tests that detect IgG antibodies to native parasitic antigens extracted from worms.

### **MAJOR ADVANCES AND DISCOVERIES**

Filarial antigens in the serum are present only during recent infection. The antigens disappear from the circulation with the clinical cure, so is absent in past infection. Therefore

demonstration of circulating antigen will be useful to distinguish between recent and past infections. Two monoclonal antibody-based ELISA that detects the filarial antigen in the serum is available. The ELISA employing monoclonal antibody AD12 detects a 200-KD antigen of adult *Wucheraria Bancroft* in the serum. ICT filariasis card test is a new and rapid filarial antigen test that detects soluble *W.bancrofti* antigens in the serum of infected humans. The test is developed by ICT Diagnostics (Bangladesh, New South Wales, Australia) and uses monoclonal antibody AD12 to detect antigens. The main advantage of the test is to read visually without the need for any sophisticated instrument. The major advantages of these antigen detecting assays are that blood can be collected during day time for the demonstration of antigen. The demonstration of antigen in the urine is the most recent approach for the diagnosis of bancroftian filariasis(33).

### **CURRENT DEBATE**

Researchers at the University of Illinois at Chicago (UIC) have developed a novel vaccine for the prevention of lymphatic filariasis.

The immune response elicited by this vaccine has been demonstrated to be protective against both *W. bancrofti* and *B. malayi* infection in the mouse model and may prove useful in the human(34) On September 20, 2007, geneticists published the first draft of the complete genome (genetic content) of *Brugia malayi*, one of the roundworms which cause lymphatic filariasis (35).

### **DIAGNOSIS**

Diagnosis of filariasis depends on the clinical features, history of exposure in an endemic area and on laboratory findings. Demonstration of microfilaria in peripheral blood. Microfilaria may also be detected in other specimens such as chylous urine or hydrocele fluid. Sometimes it can be seen in biopsy specimens. Demonstration of the adult worm in biopsy specimens. To avoid the inconvenience caused to the patient of collecting the blood at midnight, Diethylcarbamazine (DEC) provocation test can be employed. The patient is given 100mg of DEC orally and peripheral blood is examined for microfilariae in 35-45 minutes. DEC provokes the microfilariae to come in peripheral blood even during the daytime. Adult worms localized in lymphatic vessels or nodes are usually inaccessible and biopsies are usually not revealing hence are not indicated in routine laboratory diagnostic set up. In the absence of microfilaraemia, definitive diagnosis of wucheraria is difficult. In such

situations, serological diagnostic methods are useful. the tests commonly employed are haemagglutination test(Antigen derived from *Dirofilaria immitis* Fluorescent antibody test(Antigen derived from *Brugia* and other microfilaria and ELISA (Antigen derived from *Brugia pahangi*) These tests are non-specific antigens, further there is extensive cross-reactivity between filarial antigens and antigens of other helminths like a roundworm. This makes the interpretation of serological tests difficult (36) Immunochromatographic Test (ICT) Highly sensitive and specific filarial antigen detection assays, both as card test and in ELISA based format is now available for the diagnosis of *W. bancrofti* infection. The card test has the advantage that it can be performed on the blood sample drawn by finger prick at any time of the day. This test is positive in the early stages of the disease when the adult worms are alive and becomes negative once they are dead. At present no such test is available for *B. malayi* filariasis, where the detection of IgG4 antibodies is helpful (37).

## TREATMENT

When choosing between alternative treatment strategies, policy makers should also consider the costs, feasibility and acceptability, which biannual MDA leads to the strongest predicted reduction in program duration, its implementation requires additional financial and human resources in already overburdened system.(38)

There are several deworming drugs that are used to combat microfilariae infections. The drug companies GlaxoSmithKline and Merck are donating billions of dollars worth of deworming pills to the World Health Organization to help aid their plan of eradicating Lymphatic Filariasis by the year 2020. GlaxoSmithKlein's deworming pill is known as albendazole, and Merck's drug is named Mectizan. The drug of choice in the U.S. is diethylcarbamazine citrate (DEC). DEC is inexpensive to manufacture and is done so by many companies, none of which donate their product. The most effective treatment has proven to be a 2-drug combination of albendazole and DEC taken once yearly. These deworming drugs are used to kill off the circulating microfilariae, while also killing off some of the smaller adult worms. Due to the large size of the average adult worms, many of them are not killed by the current drug treatments that are provided. Because of this, the current drug treatments are used only to prevent further transmission, not to cure the already infected patient. Since the adult worm's life span is 5-7 years, the drug treatment must last 5-7 years in order to kill all living worms inside the infected host. Men can have a surgical operation to help alleviate their hydrocele by draining lymph fluid from the scrotum.



It has been shown that DEC salt is more effective than single-dose DEC in reducing the prevalence of microfilaraemia. DEC fortified salt may be useful in areas where the mobilization of the population for annual drug distribution is difficult. Common salt medicated with 1–3 g of DEC per kg is used for at least 6–12 months. It is well tolerated and safe to use in pregnancy. It is colorless, odorless, thermostable, and tastes the same as ordinary cooking salts. The macrofilaricidal effect of very low-dose DEC as used in the DEC medicated salt is not sure. Low dose DEC in salt minimizes or avoids completely the known side effects of treatment, including both acute pharmacologic effects of high doses and Mazzotti-like inflammatory reactions (probably due to dying microfilariae) induced by moderate and high doses (38).

15 endemic countries have completed their MDA programs. In some treated areas, however the decline in MF prevalence has been slower than expected. Possibly due to low coverage, mosquito vector characteristics, higher transmission efficacy between treatment regimens.(39)

Patients with tropical eosinophilia respond dramatically to DEC. Symptoms of untreated patients may resolve spontaneously, but the eosinophilia usually persists, and these patients frequently have recurrences or relapses. Broncho alveolar lavage reveals that even patients treated with DEC often have persistent mild chronic alveolitis that can cause a mild, chronic, interstitial lung disease. Steroid therapy can be used with anthelmintic therapy to lessen minor allergic reactions. Mebendazole with levamisole is a promising alternative therapy for tropical pulmonary eosinophilia patients who are allergic to DEC.

The parasites responsible for elephantiasis have a population of endosymbiotic bacteria, *Wolbachia*, that live inside the worm. When the symbiotic bacteria of the adult worms are killed by the antibiotics. DEC kills mainly the microfilariae and a less extent the adult worms. It is not effective against the third and fourth stage larvae. Ivermectin is another drug that appears to be promising in the treatment of lymphatic filariasis other drugs recently evaluated for the condition include levamisole, mebendazole, and centprazine.

According to global burden disease study, the number of infectious cases declined from 53 million in 2000 to 29 million in 2016. In same period the burden of disease in disability is declined from 1.9 million to 1.2 million(40).

## **PREVENTION**

To protect themselves against filarial infection, individuals must avoid contact with infected mosquitoes by using personal protective measures, including bed nets, particularly those impregnated with insecticides such as permethrin. Adult *W.bancrofti* does not multiply in human. Hence, to develop wuchereriosis repeated mosquito bites are essential and so avoiding mosquito bites is important. *Wucheraria* has no animal reservoir. The recommended treatment is Diethylcarbamazine (DEC) Treatment may have to be repeated in endemic areas, every two years or so. Mass chemotherapy has been tried, but it may pose difficulties in large endemic areas such as India. As DEC is non-toxic, it can be safely administered in combination with food items such as common salt.

## **CHALLENGES**

The major challenge with the currently available drugs is that the interruption of transmission requires very high treatment coverage (probably > 85% of the total population) to achieve elimination, but current approaches to drug delivery do not achieve this (only 40-60% gets treated if mass treatment is executed by the regular health services). Hence, there is an urgent need for more effective drug delivery strategies for lymphatic filariasis elimination that are adapted to regional differences and variations in health sector development(41).

## **CONCLUSION**

Very high treatment coverage (probably > 85%) is required to achieve interruption of transmission and elimination. Hence, there is an urgent need for more effective drug delivery strategies that are adapted to regional differences in India.

Control of parasitic infections depends on a number of different factors, including geographic location, public health, infrastructure, political stability, available funding, social and behavioral customs, and benefits, trained laboratory personnel, health care proper teams, environmental constraints, poor understanding of organism life cycles, and opportunities for control and overall commitment. It was considered that annual mass drug administrations together with anti-malarial activities such as indoor residual spraying had contributed to the reduction of the filarial infection. However, based on the past data obtained, we cannot exclude the possibility that filarial prevalence rates were very low or even zero originally. It is several patients with lower leg edema and pachydermic (elephant skin-like), mossy skin

lesion of the foot. Judging from clinical features and bare-footed lifestyle of people in the area, non-filarial elephantiasis, possibly podoconiosis, was suspected. This elephantiasis has been reported in areas where filariasis is not endemic(42) Current annual MDA strategies will be insufficient to achieve the 2020 LF elimination. Biannual treatment hold promise in reducing program duration, provided that coverage is good, but their efficacy remains to be confirmed by more extensive field studies(43).

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