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Review Article

LYMPHATIC FILARIASIS: AN OVERVIEW

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ABSTRACT

Lymphatic filariasis (LF) is a tropical disease caused by infection with the parasitic filarial worms: *Wuchereria bancrofti*, *Brugia malayi,* and *Brugia timori*. The symptoms of this chronic disease appear in adults (in men more than in women) and include damage to the lymphatic system, arms, legs, and genitals, which cause significant pain, reducing productivity, and social problems. LF is a cause of continued disability, pain, disfigurement, and sexual disability in the world, so the knowledge of the disease and the infection control is very important. In addition to the importance of prevention, that includes giving medicine and using controlling ways of mosquitoes. Moreover, the prevention of disease is important, that includes giving medicine and using controlling ways of mosquitoes. However, although the efforts of health organizations to reduce the LF infections, there are still many challenges including the early diagnosis and control of infection among people.

Keywords: Lymphatic filariasis, Lymphedema, Hydrocele, Mosquitoes.

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INTRODUCTION

Lymphatic filariasis (LF) is the second most common mosquito-borne disease globally. LF infection occurs by exposure to mosquito bites. There are three parasites, which cause human LF, *Wuchereria bancrofti*, *Brugia malayi,* and *Brugia timori* all of them are transmitted by *Anopheles*, *Aedes*, and *Culex*. *W. bancrofti* is responsible for more than 90% of infections globally, while *B. malayi* is mostly contributed to the transmission of the remainder. The third parasite, *B. timori*, is common in a few countries in Southeast Asia [1].

These parasites block the body's lymphatic nodes and vessels. This blockage causes fluids to collect in the tissues, which can lead to huge swelling, called "lymphedema" [2,3].

LF infection is chronic; this is due to the long life of the worms and accumulation of infection with time. Many people may be infected without being noticed, but after a long term, some people may develop severe chronic symptoms including hydrocele and lymphoedema [4].

HISTORY OF FILARIASIS

Although there are no manuscripts about LF before the 16th century, but the historical evidence of LF can be ratified through ancient artifacts which suggested that the disease may have been found about 2000 BC such as a statue of Pharaoh Mentuhotep depicting swollen limbs (Fig. 1a) [5], also the replicas of illustrations which were found on the wall tomb of Tutankhamen depicting the prince of Punt and his wife who suffer from elephantiasis (Fig. 1b) [6].

Some early scientific discoveries in filariasis history include the following

Jean-Nicolas Demarquay found microfilariae in hydrocele liquid of a Cuban in Paris (1863). In 1866, Wucherer found microfilariae in chyluria, and it was found for the 1st time in blood samples by Lewis (1872). Bancroft recognized a female adult filarial worm in the lymph node ulcer of the arm (1877). In 1877, Sir Patrick Manson, the distinguished pioneer of tropical medicine found microfilariae in the stomach of bloodsucker mosquito and later, he detected the microfilariae nocturnal periodicity (1879). The name *Filaria bancrofti* was given by Cobbold, in 1877, and the generic name Wuchereria was given in 1878. Male adult worms were found by Sibthorpe (1888) while the male filaria was found in the seminiferous hydrocele by Shichiro Hida (1903). Erwin Von Baelz detected microfilariae in the blood (1876). In Tokyo, Yushitaro Matsuura found a female adult worm in an inguinal lymph node (1896). Later, a lot of work was done in defining various manifestations of filariasis and the aim of current researches is concentrated on prevalence, treatment, transmission cycles, and newly discovered species [6-10].

EPIDEMIOLOGY OF LF

There are 120 million people in tropical and subtropical areas of the world infected with LF, about 25 million men have the genital disease (hydrocele) and almost 15 million, mostly women, have lymphoedema or elephantiasis of the leg. The total population requiring preventative chemotherapy is 57% living in the Southeast Region of Asia (9 countries) and 37% living in the African Region (35 countries) [11].

Many kinds of mosquitoes can transmit the parasite, depending on the geographic area. For example, in Africa, the most common mosquito is *Anopheles* and in the Americas, it is *Culex*, *Aedes* and *Mansonia* can transmit the infection in the Pacific and Asia.

Many mosquito bites are needed to get LF. People who live for a long time in tropical and subtropical areas are at high risk for infection while the tourists have a very low risk [12,13].

ETIOLOGY

As we stated earlier, LF is caused by three filarial nematodes of the *Filarioidea* family, *W. bancrofti* (Fig. 2a), *B. malayi* (Fig. 2b), and *B. timori* (Fig. 2c) which have generally similar life cycles and transmitted from person to person by mosquitoes: *Aedes* (Fig. 3a), *Anopheles* (Fig. 3b), and *Culex* (Fig. 3c) [7,9,14-17].

FILARIASIS LIFE CYCLE

The extrinsic life cycle starts when the microfilariae are ingested with the human blood by a bite of a mosquito. The microfilariae migrate through the gut wall of the mosquito to thoracic muscles where they become shorter and thicker, later develop into the first-stage larvae (L1). After 5–7 days, the L1 grow and develop to become the second

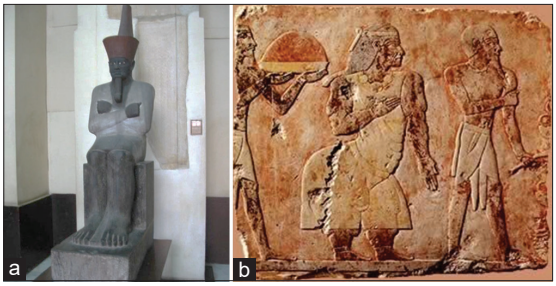

Fig. 1: (a) Statue of Pharaoh Mentuhotep depicting swollen limb [5], (b) the princess of Punt with elephantiasis [6]

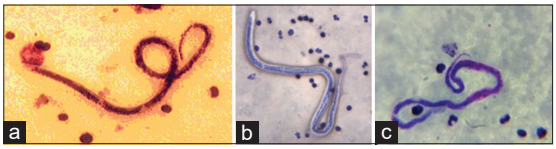

Fig. 2: (a) *Wuchereria bancrofti* [18], (b) *Brugia timori* [19], (c) *Brugia malayi* [20]

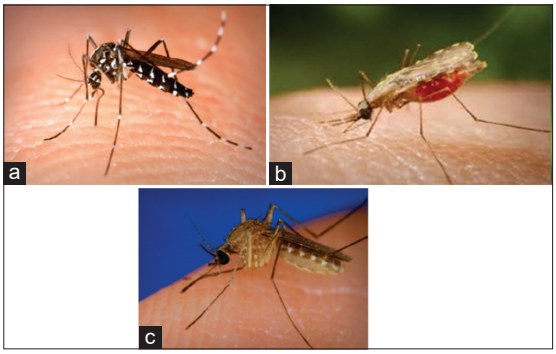

Fig. 3: The mosquitoes that transmit the disease: (a) *Aedes* [21], (b) *Anopheles* [22], (c) *Culex* [21]

stage (L2), which is more active and finally by 10–11 days, they develop to become the infective stage larvae (L3).

After maturity, most of the infective larvae (L3) move to the mosquito's proboscis, where they become ready to infect another human (Fig. 4).

When the mosquito bites the host, L3 is put on the skin surface and after pulling the proboscis; they get into the wound and travel to the lymphatics. After about 9–10 days of entering, the L3 molt to become the fourth stage larvae (L4). The L4 stage needs several days to few months before it develops and becomes an adult. The adult male of *W. bancrofti* has a length of 23.8–30.6 mm and width of 90–120 µm. The length of the female is 42.2–46.3 mm and width of 160–188 µm. In the human body, adult worms (male and female) live in lymph vessels and lymph nodes. After mating, the females produce numerous microfilariae, which migrate into the lymphatic system and spread through the bloodstream (Fig. 5) [7,8,14,18,23-25].

Symptoms

Most infected people have no symptoms and they do not know that they have LF unless tested [24]. At least half of all patients with LF are asymptomatic people. These asymptomatic infections gradually cause damage to the lymphatic system, kidneys, and disturbance in the body's immune system and this is directly linked to the efficiency of the patient's immune and may have acute inflammation of lymphatic vessels with high temperatures, chills, body aches, and swollen lymph nodes. Excessive amounts of fluid may accumulate in the affected tissues [24,27]. In chronic conditions, LF leads to lymphoedema (tissue swelling) (Fig. 6) or elephantiasis (skin thickening) (Fig. 7), and limbs and hydrocele swelling (scrotal swelling or breast swelling) (Fig. 8) and may develop to filarial abscesses [5,8,25,28-30].

Tropical pulmonary eosinophilia is another symptom of the LF infection, this is due to the high immune response to the filarial antigens, and its symptoms are excessive coughing causing in some cases chest pain due to fractures in ribs, breathlessness, and wheezing [24,31].

Diagnosis

The diagnosis of filariasis can be done by different methods such as follows:

- Blood tests: Blood counts are done, especially the eosinophils, in

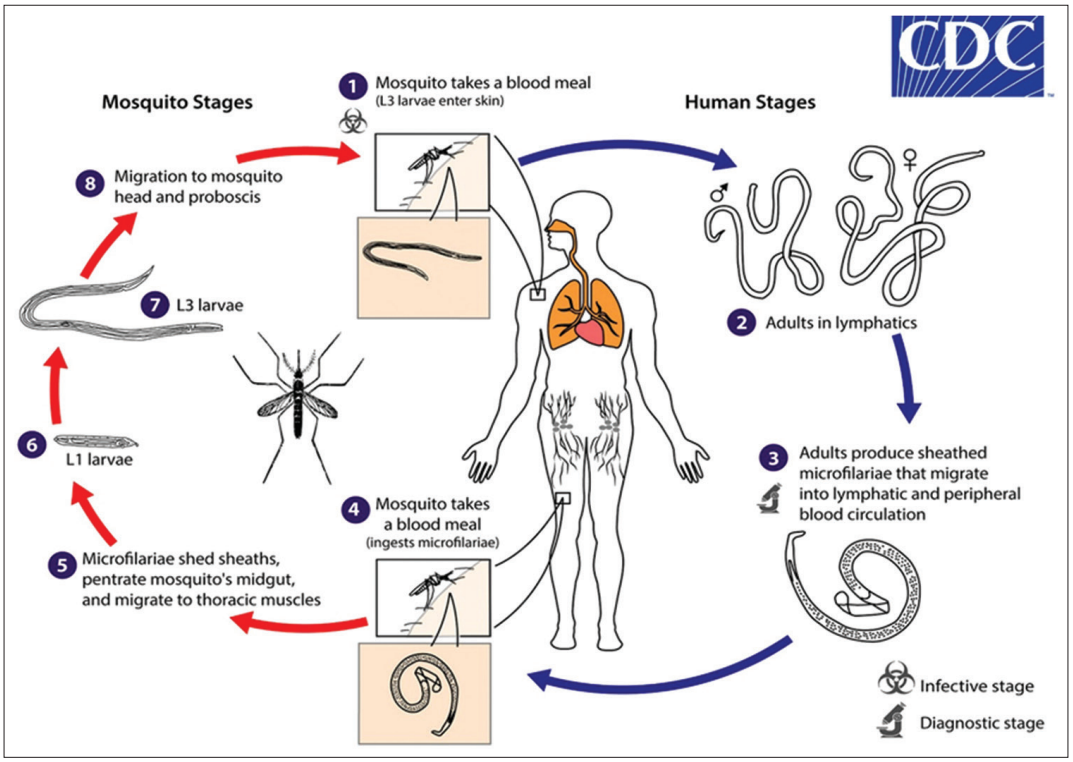

Fig. 4: The life cycle of the filarial parasite [26]

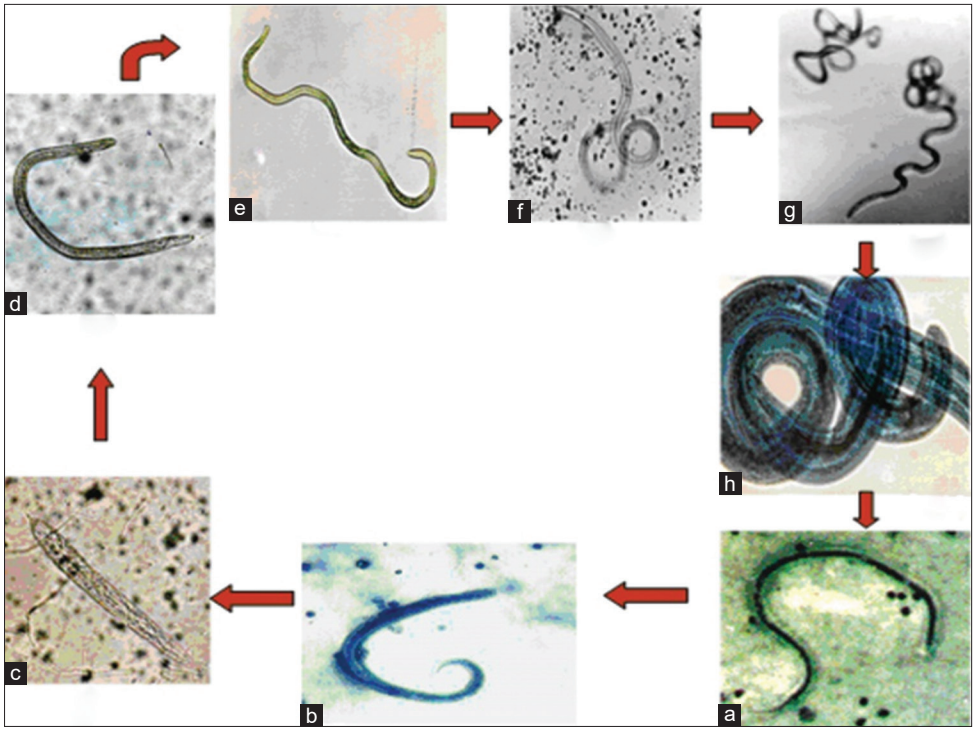

Fig. 5: (a) Microfilaria in human blood, (b) microfilaria in mosquito, (c) first-stage larva (L1) in mosquito, (d) second-stage larva (L2) in mosquito, (e) third infective stage larva (L3) in mosquito, (f) third infective stage larva (L3) in human, (g) fourth-stage larva (L4) in human, (h) adult worm in human [18]

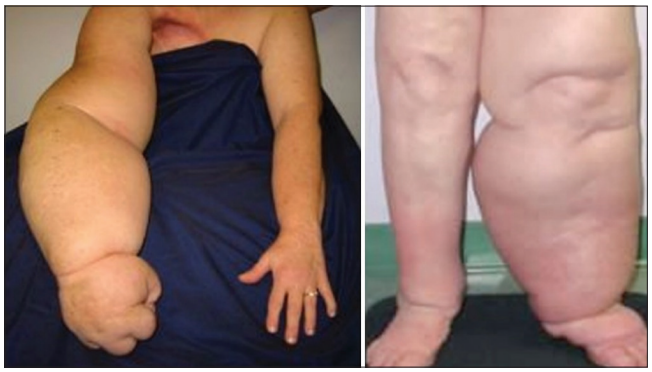

Fig. 6: Lymphedema [32]

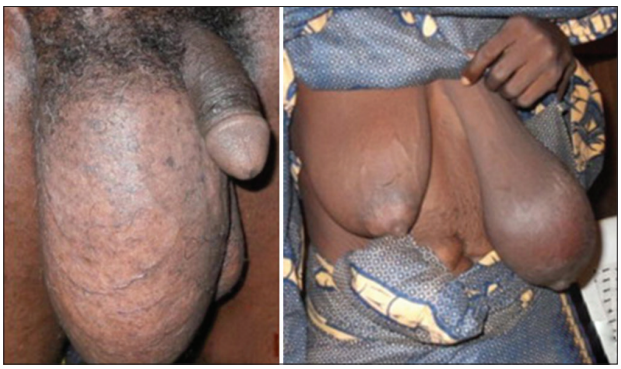

Fig. 8: Scrotal swelling and breasts swelling [34]

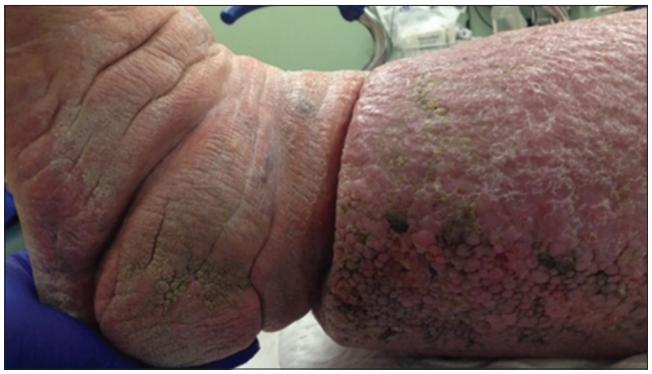

Fig. 7: Elephantiasis (skin thickening) [33]

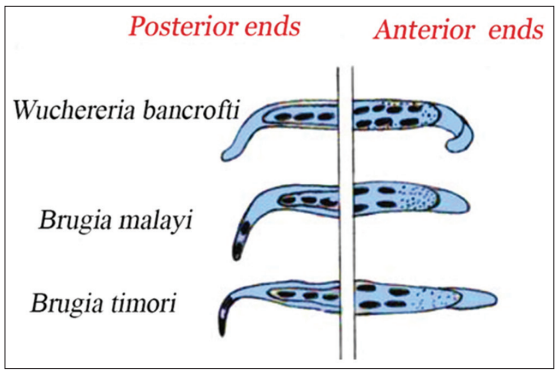

Fig. 9: Differentiation of species of filariasis larva (L3) in human [18]

addition to the identification of microfilariae in a blood sample by taking the blood at night and staining it with Giemsa or hematoxylin and eosin. Identification of the type of microfilariae is done according to the characteristics of the stage larva (L3) in human, such as the number and position of caudal nuclei, cephalic space, and the presence or absence of sheath (Fig. 9) [5,7-9,15,24,35,36].

- Identification of microfilariae in a urine and hydrocele fluid: This is done by centrifuging the fluids samples, the resulting deposits are put on a slide, and examined under the microscope [7,9,30].
- Identification of adult worms in lymphatics: The motile adult worms can be seen within the lymphatics of scrotum, breast, thigh, and the spermatic cord in infected tissue using ultrasonography [5,7,9,15,36].
- Immunological tests: Such as antigen assays (TropBio Og4C3 Test [TropBio, Australia], immunochromatographic card test), antibody assays, and polymerase chain reaction [5,7,8,9,15,24,30,37,38].

Treatment and prevention

The World Health Organization (WHO) has identified the dangerous of LF and stressed the need for early treatment to control it and to prevent further attacks. The quick diagnosis and isolation of infected patients from the endemic area result in decreasing the possibility of pathophoresis.

Treatment of LF depends on some of the drugs such as ivermectin, albendazole, and diethylcarbamazine. These drugs work to dispose of the larval worm, to hold the reproduction of adult worm and kill it. Some studies showed the killing of adult worm with treatment by doxycycline [5,8,22,25,29,30,35,39,40].

Diethylcarbamazine citrate (DEC) is the effectively used drug for treatment which is capable of disintegrating the adult *W. bancrofti*, *B. malayi*, and *B. timori* [9,25,29,30,33,35,39,40]. It rapidly disintegrates the microfilariae but disintegrates the adult worms slowly and incompletely. The use of single doses of two drugs together (albendazole with DEC) is effective by 99% in removing microfilariae from the blood for a year after treatment. Although these drugs are effective but also have side effects, these side effects may be alleviated using antihistamines and/or anti-inflammatory drugs [5,8,26]. Corticosteroids can be given along the treatment to reduce the diethylcarbamazine side effects [5,41]. It is recommended to give diethylcarbamazine to persons who do not have microfilaremia to reduce its prevalence and density [42].

In general, the efficiency of these drugs is concentrated in the early cases of the disease. In chronic cases, surgical intervention is necessary such as hydrocele surgery and lymphoedema surgery that can be classified into two main stages: Surgical operations to improve the lymph flows and excisional operations to reduce the volume of the limb [5]. Vaccines are not yet available, but in 2013, the University of Illinois College of Medicine in Chicago was reporting about 95% efficacy in testing against *B. malayi* in mice [43].

Also the effective mosquito control is very important in lessing the transmission by using the larviciding and insecticides against adult mosquitoes [7,14].

DISCUSSION

LF is a disease caused by mosquitoes in tropical regions without clinical symptoms. In the case of acute infection, patients suffer from symptoms such as inguinal lymph nodes, fever, and skin thickening while chronic LF is characterized by chronic lymphedema and swelling of the limbs, breasts, and scrotum. For treating active filarial infection is used. The disease may develop so the surgery becomes necessary. Chronic filarial disease has serious social and economic effects.

CONCLUSIONS

Considerable achievements have been made toward the LF, further studies are needed to better assess the rates of prevalence and implement control programs recommended by the WHO.

Recent studies have led to new treatment techniques, strategies, and diagnostic tools that have changed the prospects of LF control.

AUTHORS' CONTRIBUTIONS

Both authors have contributed to reviewing preparation and editing of the manuscript.

CONFLICTS OF INTEREST

We declare that there are no conflicts of interest.

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