Review Article

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Lymphatic filariasis: a snap shot of a neglected tropical disease

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ABSTRACT

Lymphatic filariasis (LF) is a leading cause of disability worldwide and one of the most crippling and stigmatizing tropical diseases. LF transmission is widespread throughout regions of West Africa, coastal and south-eastern Africa, East and South-east Asia, South western India, Western Pacific and parts of South and Central America. The disease manifests as disfiguring pathology caused by microfilariae larvae damage to lymph vessels and nodes. LF is spread by mosquitoes that have been infected with filarial nematode larvae and about a billion people in 52 countries are thought to be at risk of contracting the disease on a global scale. Complex immune responses to filaria and their endosymbionts cause the pathologies associated with lymphatic filariasis. Several studies show that non-climatic factors that may be responsible for LF transmission at the micro level include environmental, social, economic, and demographic factors. Currently, the infection is controlled by mass drug administration regimens, vector control strategies and management of morbidities. This review discusses the ecological drivers of lymphatic filariasis transmissions in endemic hotspots.

Keywords: Lympahtic filariasis, Transmission, Environmental factors

INTRODUCTION

Lymphatic filariasis (LF) is one of the 20 infections and parasitic diseases considered neglected tropical disease affecting over a billion people. It is an impediment to socio-economic development in endemic countries. LF is also one of the most debilitating and stigmatizing neglected tropical disease and a leading cause of disability globally. 1-3 It presents with chronic disabling and disfiguring pathologies resulting from damage to lymph vessels and nodes by microfilariae larvae.4-6 Other neglected tropical diseases including Buruli ulcer, trachoma leprosy, yaws and onchocerciasis, etc. cause significant morbidity with severe psychosocial consequences such as sexual disability, stigmatization and stress.⁷ Depending on the geographical location, the disease is caused by three parasitic worms, namely, Wuchereria bancrofti (W. bancrofti), Brugia malayi (B. malayi) and Brugia timori (B. timori) with W. bancrofti causing over 90% of the infections. This may also include *Culex, Anopheles and Aedes sp.*

LIFE CYCLE OF WUCHERERIA BANCROFTI

Filarial worms that cause human LF are transmitted by many species of mosquitoes. This parasite has an intrinsic and extrinsic lifecycle, thus requiring two different host systems to complete its lifecycle. The definitive host is human and the intermediate host is a blood sucking arthropod such as mosquitoes. Adults of human LF nematodes live in the lymphatic system of their host. When the adult male and female mate, the female release embryonic stage parasites called microfilaria (MF) parasites into the lymphatic system, which migrate through circulatory system into where they are available for uptake by the intermediate arthropod host. The parasites are collected in arterioles of the lung during the day and emerge at night when night biting mosquitoes are most active. The period of development and the longevity of the

parasite vary according to the species of the nematode and the mammalian host. 9-11 Estimation based on deterministic model indicates that the lifespan of adult female W. bancrofti is 10.2 years within, which the adult female is able to steadily produce MF for a minimum of 5 years. In the intermediate host, the extrinsic lifecycle of the parasite begins. They penetrate the insect's gut wall and move to the thoracic muscles where they mature (through two life stages: L1 and L2) into third stage infective larvae (L3). The MF in the mid-gut of the mosquito vector migrates through the gut wall to the haemocoel and subsequently to the thoracic muscles within about 24 hours. In the mid-gut or the haemocoel of the mosquito, the MF parasite sheds off its sheaths into larvae. The larvae grow through L1, L2, and L3 infective stages then migrate to the proboscis of the mosquito, where they can be deposited in the skin of a human host during meal time.

DISTRIBUTION OF LYMPHATIC FILARIASIS

Distribution of LF is marked by the relationship between ecological conditions, climatic elements, mosquito prowess, parasite, human population and intervention strategy. ^{12,13} On the global scale LF is endemic in about 72 countries, with the African continent having 34 endemic countries. The endemicity is extremely restricted within the tropical and subtropical countries where warm and humid weather supports the timely development of both the parasite and vector. ¹²

LF transmission is widespread throughout regions of West Africa, coastal and south-eastern Africa, East and Southeast Asia, South western India, Western Pacific and parts of South and Central America. ^{14,15} In southern and Central Africa, it is predicted that large foci (of the disease) are to be found in the northeast of South Sudan, Uganda eastern DR Congo and Southeast Zambia. ^{12,15} Globally, it is estimated that over a billion people in 52 countries remain at risk of the disease. ^{13,16}

FILARIAL INFECTION OUTCOME IS HOST IMMUNE RESPONSE-DEPENDENT

The pathologies associated with lymphatic filariasis result from complex immune responses against the filaria and their endosymbionts. ^{4,17,18} Failure to clear the larvae results in the development of various pathologies associated with filarial infection. The most prominent condition is the damage to the lymphatic vessels, which is mediated by the immune response to the adult worms living in them.

The immune responses known as lymphangitis are characterized by common clinical manifestations such as lymphoedema ((i.e., elephantiasis (skin/tissue thickening) and hydrocele (fluid accumulation in scrotum)) and acute filarial fever, resulting in considerable incapacity to the affected individuals. Repeated episodes of lymphangitis lead to the formation of fibrous and calcified tissues in and around the lymphatic vessels. However, situations where the host's immune responses are absent, microfilaremia

can persist and chances of parasite transmission are maximized.⁴

TRANSMISSION HYPOTHESIS

Lymphatic Filariasis is transmitted through the bite of mosquitoes infected with filarial nematode larvae. During a blood meal, third stage infective nematode larvae (*W. bancrofti*) enter the blood through the wound made by mosquito. The larvae then migrate to the nearest lymph gland where they mature into the thread-like adult worms within three months to one year.

To produce a new patent infection, increased and prolonged exposure to *W. bancrofti* larvae is required. The identification of high infections among older age groups by several studies confirms this fact. ^{19,20} Other studies, assessing the parasite transmission dynamics with various mosquito species in different parts of the world estimated that 2,700 to over 100,000 infective mosquito bites is required to produce a new patent infection. ⁵ A study revealed that the microfilaremia are rarely found in younger children. ²⁰

In children, the infection was known to be asymptomatic and not clinically perceptible until they are four or five years. But other findings are showing that there is development of clinical manifestation among children. ²¹ Although people are affected in all ages men are increasingly inclined to showing symptoms, while females show more resistance to the infection. ²²

ENVIRONMENTS OF OCCURRENCE

Research has shown that non-climatic factors that may be responsible for LF transmission at micro level may include environmental, social, economic and demographic factors.²³

Coastal environments

While geographical distribution of LF endemicity varies significantly, field observations suggest some common similarities from one region to the other. For instance, in India the high endemic districts are situated along the eastern and western coastal belt and river basins, whereas the low endemic areas are situated at the interior plains. ²⁴ Interestingly in Ghana wetlands areas have been implicated to contribute to the transmission of the disease. While this has not been comprehensively documented in many endemic areas, it is interesting to note that transmission of LF is predominately along coastal regions in many countries.

Having indicated this, it is also key to suggest that there are some areas where this might not follow the normal conversion, and thus LF may occur in places with little or no wetlands. ¹⁴ A study on the regional distribution of LF in Nigeria found mangrove and freshwater swamps not suitable for transmission of LF. ²⁵ This may be due to the

presence of fishes in these mangrove and freshwater swamps that could be feeding on mosquito larvae, thus reducing the abundance of the vectors.

Swamps and mangrove environments

Mangrove ecosystem grows on tropical and subtropical coastal areas. Due to its poor sanitation they may be suitable breeding grounds for mosquitoes. This ecosystem is rich in detritus and high in organic content, which may provide good feeding places for mosquito larvae. Swamps were areas around mangroves that were located relatively far from settlement. Coastal wetlands in the southwest of the western region of Ghana are predominantly mangrove swamps. This type of vegetation provides habitat for fish and other wildlife. There is scarcity of information on LF with this vegetation in Ghana.

Several investigations found that undisturbed mangrove areas had more mosquitoes with mosquito biting patterns only in the dawn and dusk, while the disturbed mangrove had less number of mosquitoes with irregular biting pattern throughout the day.²⁷ In the undisturbed mangrove areas, particular species like *Wyeomia sp.* were found to be present, while more than one species were found in undisturbed mangrove areas.²⁷ Another study also found that amount of industrial land and percentage of mangrove was positively related to mosquito abundance and mosquito species richness.²⁸ Until now, there has not been any proof yet of LF being found in swamp and mangrove environments.

Landcover modifications

The use of landuse and landcover changes like urbanization, irrigation, agriculture, deforestation have effect on the distribution of LF due to the possibility of generating suitable vector habitat. ^{29,6,30} It has been found that a high probability of infection was associated with croplands and grasslands and that areas with human adaptation to the landscape seemed to influence the general presence of LF. ¹⁵

In the southwestern zone of Nigeria LF was high in communities with less tree coverage and canopy height. ³⁰ Landcover and landuse change from rainforest to oil palm plantation influenced the abundance and distribution of *Aedes* vectors in the south-eastern Côte d'Ivoire. ³² Similarly, LF prevalence was increased during Malaysia's swift economic growth (in the past decade) due to the environmental changes as a result of agricultural practices like rubber, oil palm and rice plantations. ³³

Agricultural and irrigation environments

Adverse effects of water impoundments (example, dams for hydroelectric power, irrigation, etc.) can threaten human health.^{34,35} In Ghana, it has been known that communities with LF were areas where dams were built

for agriculture; and these were of high endemicity of W. bancroftian infection.³⁶ For example, the Okyereko Irrigation Project, which was constructed in 1974 for agriculture crop production sustainability provoked intense malaria transmission.³⁴ and clinical manifestation of bancroftian filariasis (with 32% hydrocele and 36% limb elephantiasis).³⁰ The study concluded that irrigation projects were responsible for increased transmission of bancroftian filariasis.

Water impoundment meant for both cattle and agricultural productivity in the Tono (in the Upper East region of Ghana), Vea (in Bolgatanga) and Kogo (near Vea) reservoirs enhanced transmission of the Bancroftian filariasis in the surrounding districts (Kassena Nankana, Bolgatanga and Bawku) in the Northern region of Ghana.²⁹ The study showed that annual transmission bites were higher in the irrigation communities. The Omi dam irrigation in the Omi community of the Kogi State of the North Central Nigeria presented a similar situation.³⁷

It is reported that irrigated rice fields in Africa enhanced the breeding of *An. Gambiae* and *An. Funestus* with less of C. quinquefasciatus.³⁵ Similarly, certain parts of Africa endemic for *W. bancrofti* infection were also areas where dams had been constructed.³⁸

Socio-economic environments

As outlined above, socio-economic developments, which lead to changes in the landcover/landuse have a great influence on the transmission of vector-borne diseases. Occurrence of filariasis at the individual or community level depends on human (demographic) factors.²⁴ Such demographic determinants may include population density, movement, economic status, sanitation, education level etc. Age and gender are said to influence level of exposure to the disease parasite.

LF makes individuals unable to engage in economic activities and is correlated with chronic poverty levels in endemic countries. A parasitological, clinical and entomological survey for LF in towns and villages along the coast of Ghana found more males than females with the parasite. Socio-economically deprived communities on the coastal and poor regions of Ghana have records of higher LF prevalence. The major impacts of LF occur in poor rural areas with only negligible prevalence in towns around such places.⁶ Attempts therefore to reduce inequalities in health have led to services targeted at more deprived communities in the country.

Overcrowded environments

Human population density has been considered a risk factor in LF prevalence.^{39,40} Human to vector density ratios are important drivers of the transmission of vector-borne infections. Elsewhere, the increase or decrease and spread of infection have been shown to be related to variations in population density rather than climate change.^{39,40}

Seasonal variation

Lymphatic filariasis depends on the geo-environmental variables (physiographic and climatic) at macro level.^{24,41} Using a geo-environmental risk model, a range of values for altitude, temperature rainfall, relative humidity have been identified as conducive for the transmission of filariasis in Tamil Nadu region of Southern India.²⁴

It has been established that there is proliferation of mosquito vector density during rainy seasons.¹⁵ Studies regarding the frequency and seasonal variations of acute filarial attacks among LF patients in the Ahanta West district of Ghana revealed that seasonal variations of filarial attacks among lymphoedema patients is highest in the rainy season, probably due to increase in the rate of infective bites from mosquitoes, which is known to be influenced by rainfall patterns.⁴²

In Nigeria it was found that precipitation during the driest quarter contributed most in sustaining transmission and that at higher temperatures LF occurrence declined.²⁵

In India and Africa, filariasis infection prevalence has been attributed to altitude, which influences both vector survival and parasite development and survival. ⁴³ Temperature also affects the rate at which parasites develop within the mosquito. The frequency at which a mosquito takes blood meal and the survival of the infected LF endemic areas are usually within a temperature range of 22–30°C. ⁴⁴ At temperatures below 22°C microfilariae penetration in the gut of the mosquito is reduced and little or no development occurs. ⁴⁵

TREATMENT AND CONTROL

Mass drug administration

In the year 2000, a large scale global programme to eliminate LF dubbed Global Programme to Eliminate Lymphatic Filariasis (GPELF) coordinated by the World Health Organization (WHO) was launched with the hope that repeated mass administration of microfilaricidal drugs to 65% or more of the population at risk would reduce microfilaria density to the point of interrupting transmission and subsequent eradication of the disease. It also encouraged the mapping of the global distribution of LF. It has been suggested that since risk factors related to the disease vary in endemic areas the disease is focal which also implies that intervention programmes should be specific and targeted in endemic areas.⁴⁶

The GPELF involves a yearly distribution of microfilaricidal drugs constituting single doses of 400mg of Albendazole (ALB) plus either 150 – 20 mg/kg of Ivermectin (IVM) or 6 mg/kg of Diethylcarbamazine (DEC) administered together for 4-6 years. Before the beginning of this programme, DEC had been used treatment of LF over the past 35 years.⁴⁷ Also, natural remedies such as exclusive use of table salt or cooking salt

fortified with DEC for 1-2 years has been recommended and implemented in a few areas. 48

Since year 2000, the programme has delivered more than 7.1 billion treatments to over 850 million people at least once in 66 countries to stop the spread of infection. ¹⁶ MDA is estimated to have cured or prevented up to 96 million new cases of LF and averted more than \$100 billion of lifetime economic loss. Although microfilaricidal drugs have little or no direct benefit to infected individuals with clinical conditions, the number of new elephantiasis and hydrocele cases as a result of LF has declined by about 72% since year 2000.⁴⁹

Morbidity management

Once infected the clinical LF conditions can only be managed by proper hygiene including regular washing with soap and water to prevent further bacterial infections. Exercising, appropriate footwear and raising the infected leg to reduce the frequency of acute attacks are other forms of management.⁵⁰ Enlargements caused by W. bancrofti infections are usually unilateral and the incapacitating deformities often require surgery to remove the surplus fibrous and calcified tissues. The economic impact of LF pathologies is huge given that it normally affects individuals living in poor rural areas with limited access to quality health care. In attempt to reduce the impact of morbidity associated with the disease, many countries have adopted several morbidity control programmes. While this programme offers significant contribution to reducing the burden they are mostly unsustainable because they are foreign donor dependent in many countries. However, the case of successful intervention in Gambia could be attributed to the extensive national use of bed nets.51,52 Housing and sanitary improvement have been suggested (in some cases) to be a means of offering protection against LF transmission in endemic communities.⁵³

CONCLUSION

Every year the management and control programs against human filarial infections cost millions of dollars, but elimination timelines have eluded most countries with the existing control strategies. The two most clinically important nematode infections, i.e. lymphatic filariasis and onchocerciasis have been earmarked to be eradicated by the end of the years 2020 and 2025, respectively. However, this appears to be impossible given the current infection prevalence in most endemic countries. This implies, eradication of these nematode infections in the future will require stringent monitoring of all possible causative risk factors. It has been established that several climatic and environmental factors play significant role in the transmission of LF. Interestingly, proliferation of mosquito vector density during rainy seasons and low altitude influences both vector survival and parasite development and survival. Distribution of LF is marked by the relationship between ecological conditions, climatic elements, mosquito prowess, parasite, human population and intervention strategy. This makes the management of the disease very complex in addition to its already compounded life cycle.

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