Lymphatic Filariasis: A systematic review on its morbidity and road to elimination

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1. Introduction

Lymphatic filariasis (LF) is a vector borne disease caused by majorly three nematodes within family Onchocercidae including Wuchereria bancrofti, Brugia malayi and Brugia timori, which are transmitted by mosquitoes. According to World Health Organization (WHO), W. bancrofti is responsible for nearly 90% of LF infections worldwide. On the contrary, B. malayi is prevalent only in some parts of South and Southeast Asia, and B. timori is found only in Indonesia (World Health Organization, 2020). Disease is endemic in 72 countries with more than a billion people are at risk of infection and some 51 million people are clinically affected worldwide (World Health Organization, 2020).

LF is identified as a Neglected Tropical Disease (NTD) by WHO. Chronic symptoms of LF are disfiguring and burdensome, creating social liability and poverty. The epic body therefore set goals for its control and management by year 2030. Considering the Sustainable Development Goals (SDG) 2030 set by United Nations * Corresponding author: Muhammad Manjurul Karim, Department of Microbiology, University of Dhaka, Dhaka 1000, Bangladesh. E-mail: manjur@du.ac.bd

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(UN), this review summarizes current status of filariasis worldwide, available diagnostic procedures—conventional and modern, recent advances in anti-filarial treatment including conventional practices and their pros and cons, and different control strategies with special emphasis on MDA citing the efforts taken by Bangladesh en route to its elimination.

2. Clinical manifestation

LF begins asymptptomatically and develops to elephantiasis. Progression of asymptomatic LF to symptomatic LF is influenced by factors like host’s immune response and cumulative acquisition of worms (Freedman et al., 1994). Although more than half of filarial infections are asymptomatic, lymphatic abnormalities do develop. A study in India revealed abnormalities in lower limb lymphatics in 63.5% of 52 asymptomatic children (Kar et al., 2017).

The most frequent acute clinical signs of LF are Acute Dermato-Lymphangio-Adenitis (ADLA), which are generally accompanied by fever, chills, headache, discomfort in affected region, and vomiting. In severe instances however, there may be toxemia, altered sensorium, and urine incontinence (Shenoy, 2008). ADLA attacks are linked to secondary infections by bacteria, such as group A streptococcus, which cause inflammations of lymph glands (lymphadenitis) and lymph channels (lymphangitis) as they gain access to lymphatics that have been affected and dysfunctional due to filarial infection, resulting in ADLA attacks and afterward lymphedema (Suma et al., 1997). Skin lesions established by fungal infection in interdigital spaces, injuries or infections in foot facilitate passage of such bacteria into afflicted limbs (Shenoy et al., 1995). A cute attacks become more frequent as disease progress and abet development of lymphedema (Shenoy et al., 1996).

Human might develop hypersensitivity response known as tropical pulmonary eosinophilia (TPE) to filarial antigens of W. bancrofti and B. malayi (WEBB et al., 1960) with low frequency (<0.5%) in endemic areas (Lymphatic filariasis: the disease and its control, fifth report of the WHO Expert Committee on Filariasis, 1992). TPE is characterized by high eosinophilia levels (>3,000/μL and may rise as high as 80,000/μL), asthma-like symptoms and restrictive lung disease (Boggild et al., 2004). Antigenic components released by degenerating microfilariae trapped in pulmonary microcirculation elicit an immunological response and eosinophil degranulation, resulting in a severe eosinophilic inflammation affecting lower airways (Nutman et al., 1989; and Udwadia, 1975).

Hydrocele, a secondary disorder to LF, is a painless expansion of scrotum in adult males mostly caused by W. bancrofti (Debas et al., 2015; and Norões and Dreyer, 2010). Migration of adult worm and their persistence in scrotal lymphatic system leads to clogging of lymphatic system and hydrocele. A cute hydroceles are caused by death of filarial worms, which typically occurs after medical treatment. Inflammatory response to dissolving worms causes a temporary lymphatic obstruction (Addiss and Brady, 2007; and Noroes et al., 2003). W. bancrofti is the most commonly associated filarial parasite with a chronic clinical presentation caused by a dysfunctional hydrocele lymph system as adult worms migrate to scrotal lymphatics and form scrotal nodules (Debas et al., 2015; and Norões and Dreyer, 2010).

Lymphedema of limbs is a typical chronic symptom of LF that progresses to elephantiasis. In early stage, damage of limbs by lymphedema is reversible but skin thickens and folds in severe lymphedema, typically with hypertrichosis, black pigmentation, nodules, warty development, intertrigo in webs of toes, or chronic non-healing ulcers (Burri et al., 1996).

3. Epidemiology

LF was endemic in 72 countries with an estimated case number of about 198 million people worldwide before Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000 was in effect (Figure 1). On the 20th year, although GPELF could not achieve its original goal, 48 out of 72 endemic countries were considered to require MDA in the year 2020. While 8 countries stopped the MDA program, 17 countries eliminated LF resulting in the reduction of the disease burden by 74%, to an estimated 51 million globally (Mathew et al., 2020; and Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021) (Figure 1). South East Asian region (SEAR) has the highest burden of LF, estimated more than 36 million cases, that accounts more than 70% of all global cases with around one million lymphedema patients and half a million of hydrocele patients in nine countries (Deshpande et al., 2020). According to report of WHO on LF in 2020, although three out of nine endemic countries of SEAR are declared free of LF and one has stopped MDA program, near 500 million people required MDA in SEAR which is 58% of global MDA requirement (World Health Organization, 2020).
African region has the second highest number of LF cases in the world, having more than 10 million cases with 148,115 active lymphedema and around 137,696 hydrocele patients (Deshpande et al., 2020). Currently, more than 339 million people of this region requires MDA. Notably, Equatorial Guinea and Gabon, 2 out of 36 endemic countries, however have not started any MDA program (Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021).

4. Diagnosis

Strategy of diagnosing and treating filarial infections varies depending on geographic location and availability to medical resources, and depends on a combination of clinical, radiographic, and laboratory diagnostic techniques (“CDC - Lymphatic Filariasis - Resources for Health Professionals,” 2017; and Centers for Disease Control and Prevention, 2017a, 2017b). In endemic areas, objectives of early diagnosis are minimizing long-term illness consequences, monitoring, and treatment of infection. While diagnosing, it is important to establish patient’s history of vector exposure because short periods of exposure, such as visiting an endemic area will not lead to high levels of microfilaria, as opposed to prolonged exposure, such as living in an endemic region. There are various techniques for diagnosing LF:

Microfilariae detection: Identification of microfilariae in peripheral blood on dyed thick and thin blood films has long been used to diagnose most filarial nematode infections. Considering microfilariae’s periodicity, venous blood is collected when microfilaria levels are maximum, for example, a night time is preferred for W. bancrofti and Brugia spp, while day time is suitable for Loa loa, a filarial nematode that causes loasis (Mathison et al., 2019; and Nanduri and Kazura, 1989). Capillary blood from periphery exams, which contain more microfilaria from W. bancrofti and Brugia spp than venous blood can be performed through finger pricks in addition to venous blood samples (Global Health, 2017; and Nanduri and Kazura, 1989). Microfilaria detection was extensively utilized in endemic regions across the world until development of immunological tests. Major disadvantages of this method are its periodic nature and the fact that it only works till lymphedema develops (Mendoza et al., 2009).

Serologic Assays: An array of serological techniques targeting either antigen or antibodies is developed on field for diagnosis of LF including Enzyme Linked Immunosorbent Assay (ELISA), Luciferase Immuno Precipitation System (LIPS) and multiplex bead assay and Immune-Chromatographic Test (ICT) to avoid inconvenient night sampling.

Detection of antigen: First commercial W. bancrofti antigen test kit was based on monoclonal antibody Og4C3 (Trop-Ag W. bancrofti ELISA kit, JCU Tropical Biotechnology Pty Ltd, Queensland, Australia); it detects Circulatory Filarial Antigen (CFA) in ELISA (Moreand Copeman, 1990; and Weil et al., 1997). This test results negative for patients of Onchocerca volvulus and B. malayi (Harnett et al., 1999; and More and Copeman, 1990).
Although, this test can detect circulating antigen in 94–100% microfilaria carriers with high specificity, it is not used in regular diagnosis for its high cost (Harnett et al., 1999; and Nicolas, 1997). On the contrary, a rapid ICT based assay, filariasis card test that uses mAb A D12.1 takes only 5–15 min to complete without any specialized equipment and gives comparable results to ELISA at low cost, hence is popularly used for diagnosis (Weil et al., 1987, 1997). B. malayi has no antigen detection-based test used in routine diagnosis of LF (Harnett et al., 1999). Multiple ELISA-based detection tests were developed to detect antigen of O. volvulus from blood and urine with specificities varying from 86% to 98%; as they corroborate high incidence of false positive, these methods are not used in regular diagnosis (Cabrera et al., 1989; Mbacham et al., 1992; and Schlie-Guzmán and Rivas-Alcalá, 1989).

Antibody detection: Antibody detection assays for LF was not well explored until development of ELISA and Radioimmunoassay (RIA) as they compensated for major drawback of most filarial antigen detection tests, the cross reactivity (Hamilton, 1985). Initially studied recombinant antigens from B. malayi, W. bancrofti had specificity issues (Dissanayake et al., 1992; Harnett et al., 1999; and Theodoret et al., 1993). An ELISA (CDC, Atlanta, GA) for IgG4 antibodies against recombinant Bm14 antigen has showed relatively high sensitivity (92%) and specificity (99%) in detection of B. malayi infection (Chandrashekar et al., 1994; and Won et al., 2018). Recently developed Wb123-based IgG and IgG4 LIPS assays can detect W. bancrofti infection with 100% sensitivity and 98% to 100% specificity (Kubofck et al., 2012; and Won et al., 2018). Such detection assays can give accurate result in a relatively short time that makes them suitable for epidemiological surveys however, requirements of specialized equipment and trained personnel as well as high cost thwart its use in regular diagnosis.

X-ray and Ultrasound detection: Characteristic movement of living adult filarial worms of W. bancrofti, known as “filarial dance sign” in scrotal lymphatics is detected using ultrasonography having a 7.5 or 10 MHz probe (Arid, 2021; Panditi et al., 2016; and Singh et al., 2019). This method is suitable only for asymptomatic males with microfilariaemia, and not useful once lymphedema develops (Freedman et al., 1994). B. malayi parasite can be detected in lymphatics of thigh, epitrochlear region, axilla, and popliteal fossa but not in scrotal lymphatics (Mendoza et al., 2009; and Shenoy et al., 2007). X-ray can identify calcified remains of the worms in the tissue, however its use is limited as it only detects dead adult worms (Mendoza et al., 2009).

Polymerase chain reaction (PCR) assay: PCR as well as Real Time PCR-based diagnosis of LF are available with primers mainly targeting multiple repeat sequences in chromosomal DNA (Dissanayake et al., 1991; Fischer et al., 1999; McCarthy et al., 1996; Rao et al., 2006; and Williams et al., 1988). These techniques can be applied for blood and urine, from where parasites can be detected and differentiated (Ximenes et al., 2014). A very sensitive and specific PCR detection method, based on a highly repeated DNA sequence of W. bancrofti (SspI repeat) was developed in 1996 by Zhong et al (Nuchprayoon, 2009; and Zhong et al., 1996). However, it showed less sensitivity when compared to Og4C3 antigen-based ELISA assay in an epidemiological study in Thailand (Nuchprayoon et al., 2001). A semi-nested PCR that can detect as little as 0.001 fg of W. bancrofti DNA in blood sample produced 100% positive results on serum and urine samples collected from participants with positive in ICT card test (Kanjianavas et al., 2005; and Ximenes et al., 2014). Hha1 repeat based PCR assay can detect B. malayi infection with high sensitivity and specificity (Williams et al., 1988). Real Time PCR assays are available for both brugian and bancroftian filariasis (Nuchprayoon, 2009). Nuchprayoon et al developed an assay to differentiate filarial parasite at species level for W. bancrofti, B. malayi, B. pahangi, D. immitis, and D. repens making useful to diagnose and differentiate parasites in endemic areas with multiple causative agents and this assay consists of a PCR followed by RFLP analysis based on first internal transcribed spacer (ITS1) along with flanking 18S and 5.8S rDNA (Nuchprayoon et al., 2006; and Nuchprayoon et al., 2005).

5. Treatment

Lymphatic filariasis patients may present an asymptomatic infection. A cute and chronic manifestations and ADA lead to elephantiasis which is incurable disfigurement of body parts specially limbs and genitals. Proper treatment of LF is necessary to prevent such complications and further spread of this illness. WHO recommended drugs include Diethylcarbamazine (DEC), Ivermectin, and Albendazole. These can be used for MDA programs too.

Diethylcarbamazine (DEC): DEC is effective in controlling all kinds of filarial parasites in blocks 2 and onchocerciasis (Mendoza et al., 2009; and Tisch et al., 2005). The recommended dose is 6mg/kg of body weight (Global Health, 2017; and Kazura et al., 1993) which is effective for lowering microfilariae levels in blood, and
the impact lasts for a year. MDA of DEC has successfully reduced not only microfilarial infections, but also its prevalence more than 50% in South India (Yuvraj et al., 2008). Because of immune response to dying microfilariae, or lipopolysaccharide released from endosymbiotic Wolbachia spp, DEC usage may induce minor and self-limiting side effects such as fever, headache, myalgia, sore throat, or cough (Mendoza et al., 2009). These reactions are more severe with onchocerciasis and loiasis which might require antipyretic or anti-inflammatory treatment.

Ivermectin (IVM): Ivermectin, a synthetic macrocyclic lactone molecule is used as a broad spectrum antiparasitic drug to treat a variety of parasitic diseases such as LF, onchocerciasis and loiasis, as well as scabies, pediculosis, demodecidosis, and strongyloidiasis (Mendoza et al., 2009). A single dosage of IVM at 150–400 mg/ kg body weight quickly reduces the amount of microfilaria in blood, for example, 90% of bancroftian filariasis (Cao et al., 1997; and Tisch et al., 2005). However, efficacy is temporary because IVM only kills microfilaria not adult worms, hence repeated course is necessary (Mendoza et al., 2009; and Tisch et al., 2005). Although in Cameroon, encephalopathy and neurologic decline were reported in only 1.83% of 50,929 patients after IVM treatment, in most cases side effects are mild and temporary (Mendoza et al., 2009; and Twum-Danso, 2003).

Albendazole (ALB): Albendazole is a broad-spectrum anthelmintic drug that only kills adult filarial worms. ALB is prescribed at doses of 400 mg twice daily for two weeks resulting in gradual decrease in microfilarial levels over the next six months (Gyapong et al., 2005; and Tisch et al., 2005).

Anti-wolbachial therapy: Wolbachia bacteria and filarial parasite have a symbiotic relationship. Use of antibiotics such as doxycycline against Wolbachia is a new strategy found effective against both bancroftian and brugian filariasis. Doses of doxycycline could be 200 mg/ day in a 4-to-8-week course. A 4-week course in Ghana demonstrated 80% reduction of microfilariae of bancroftian filariasis patients (Debrah et al., 2007). A randomized trial of doxycycline treatment for B. malayi-mediated LF in Indonesia yielded 98% reduction of Wolbachia loads after four months, and a microfilarialaemia reduction up to 87% after one year (Supali et al., 2008).

Combination therapy: Drug combinations are increasingly being used for treating LF in endemic areas. A single dosage of DEC in conjunction with either ALB or IVM was found more effective than DEC alone. In a randomized community-based trial in Papua New Guinea, reduction up to 91.1% in microfilarial intensity was evidenced in a combination therapy than with DEC alone that reduced 57.5% cases (Bockarie et al., 1998). Furthermore, yearly transmission potential fell from 75.7 to 98.8% in areas receiving combination treatment, compared to 75.6 to 79.4% in those receiving DEC alone (Bockarie et al., 1998). A single ALB dose plus IVM has the most sustained effect on microfilaraemia (Ismail et al., 1998). This combination effectively reduced microfilarial prevalence to 87-88% of the baseline at 7–12 months post-treatment (Beach et al., 1999). Combination of DEC and ALB appears to have the highest macrofilaricidal impact (Ismail et al., 1998). Doxycycline, in combination with DEC and ALB has also been proven effective in decreasing microfilaraemia (Supali et al., 2008; and Turner et al., 2006).

Management and surgical treatment of lymphedema: Lymphedema is an irreversible condition for which there is no known treatment. In the early stages of lymphedema characterized by occasional swelling and acute attacks of lymphangitis, treatment with anti-filarial drugs was shown just prophylactic for patients (Dreyer et al., 2001). As skin-folding develops, patient requires additional treatment to prevent ADLAs which was mostly related to secondary bacterial infection (Suma et al., 1997). Proper hygiene of the infected areas is important to prevent ADLAs, that can be accomplished by washing the affected area with soap and water twice a day; keeping the area dry; clipping nails; and trying to prevent or promptly treat any local injuries or infections (Ciocon et al., 1999; Dreyer et al., 2001; and Palumbo, 2008). Resting legs at elevated position, use of an elastocrepe bandage, or tailor-made stockings, exercise, massage of affected limb and heat treatment can provide relief and may prevent further swelling progression (Chang et al., 1989; Dreyer et al., 2001; and Palumbo, 2008).

Surgery for lymphoedema of limb can be classified into two main types: bypass procedures and debulking operations (Tiwari et al., 2002). Although men showed less improvement than women after debulking operations, overall, bypass procedures have showed promising outcome (Miller et al., 1996; and Tiwari et al., 2003).

6. MDA en route to LF Elimination

LF is an NTD that affects a large number of people in impoverished community. Chronic symptoms of LF are disfiguring and burdensome, accounting for an estimated 5.25 million disability-adjusted life-years (DALYs)
and at least US$ 5.7 bn in yearly economic loss (Mathew et al., 2020). International Task Force for Disease Eradication (ITFDE) listed LF as one of six infectious illnesses designated as “eradicable” or “possibly eradicable”. GPELF was formed with two goals in mind: limit spread of LF by MDA and relieve suffering of afflicted patients through morbidity management and disability prevention.

On the 20th year, although GPELF could not achieve the set goals, it could able to eliminate LF in 17 countries, stop MDA program in eight countries while 48 countries continued its operation out of 73 endemic countries by the year 2020 with 86.3% of implementation units (IU) achieving effective coverage globally (Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021). Since 2000, more than 8.6 billion treatments were administered to over 925 million individuals worldwide (Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021) resulting in the reduction of incidence by 74%, to an estimated 51 million (Mathew et al., 2020). 649.1 million persons were out of MDA, representing a 43% reduction from the total population living in IUs that were considered endemic, indicating continued progress in effect towards achieving SDG goal 3.3 (World Health Organization, 2020). Population receiving MDA in 2020 was 863.2 million, with 358.8 million persons treated (41.6%), a 34% decrease from 2019 owing to COVID-19 pandemic (Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021; and World Health Organization, 2020).

South East Asian region (SEAR) has the largest LF burden, with just India accounting for more than half of the world LF burden in 2020 (Figure 2) (Kapa and Mohamed, 2021; and Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021). SEAR nations formed National Programs to Eliminate LF (NPELF), with 2020 as target date. By 2020, 91.8% of IUs achieved effective coverage and three countries including Maldives, Thailand and Sri Lanka were declared free of LF and Bangladesh been under post MDA surveillance (Figure 2).

Bangladesh strategy for eliminating LF: Bangladesh was formerly one of the countries having the largest number of LF victims. Despite being a low- to middle-income country, Bangladesh shines out in SEAR due to the best practices implemented by the NPELF. Filariasis Elimination Program was launched on 9th November, 2001 with implementation of the first MDA (Khanum et al., 2013). Each of 19 endemic districts was designated as an IU for MDA targeting around 35 million people. By 2010, LF program effectively gave at least three rounds of MDA to each of the 19 endemic districts, with 12 districts getting more than six rounds of MDA, totaling more than 150 million doses to the target population (Hafiz et al., 2015; and Shamsuzzaman et al., 2017). Transmission Assessment Surveys (TAS) 1 was implemented in five districts in 2011, and by 2016 all endemic districts were under TAS1, and MDA program in all IUs was terminated following satisfactory achievement (Shamsuzzaman et al., 2017; and Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021). Second round of TAS (TAS2) was implemented from 2013 to 2018 (Kapa and Mohamed, 2021). Its third round (TAS3), scheduled to be completed by 2020 was interrupted due to COVID-19 pandemic, however survey duration was extended to 2021 (Weekly epidemiological record Relevé épidémiologique hebdomadaire, 2021).
7. Conclusion

Despite the fact that, GPELF’s 2020 aim was not met, the globe has made remarkable progress toward LF eradication and has already lowered disease burden dramatically. Both MDA and TAS were halted due to Covid-19 pandemic that specifically postponed 167 surveys in SEAR alone until 2021. Despite a catastrophic global pandemic, progress was achieved throughout GPELF in 2020, and in order to meet NTD road plan objectives for 2030, WHO is pushing countries to continue MDA and TAS utilizing enhanced MDA delivery systems, as well as extend access to necessary treatment for lymphedema patients.

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