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New Perspective of Lymphatic Filariasis-Towards Elimination

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ABSTRACT

Lymphatic filariasis (LF) is an important public health problem globally as well as in India. LF causes both acute and chronic morbidity with significant impediment to socio-economic development. The aim of this review was to analyze the current scenario in filariasis research. This debilitating disease which carried a serious social stigma and once thought to be difficult to treat, control, and eradicate, now could achieve significant success in its treatment and elimination globally by 2020, including from India. Achievement of success so far could be possible through series of evolution in understanding pathology of the disease, pathogenesis of the etiologic agent parasite, diagnostic tools, therapeutic and preventive approaches through new knowledge, techniques and development of investigative tools.

Keywords: Lymphatic filariasis, *W.bancrofti,* lymphedema.

Introduction

Tropical and vector-borne diseases are a challenge to the community as they impose a relatively high degree of social impact on the financial and economic resources and disturb the affected patients psychologically. Lymphatic filariasis (LF) is a tropical disease which is prevalent in the developing countries and least developed countries. The aim of this review was to analyze the current scenario in filariasis research. The focus is to depict the contribution of India and its impact on the global filariasis research.

Global Scenario

LF caused by three parasitic species of nemotode parasites like *Wuchereria bancrofti* (*W.bancrofti*), *Brugia malayi* and *Brugia timori*, characterized by chronic morbidity in the form of hydrocele, lymphedema and elephantiasis, and is considered a major public health problem that belongs to group of neglected tropical diseases (NTDS) globally (1).

While 1.34 billion people are at risk of this mosquito-borne disease globally, large majority (65%) are shared by south East Asia (2). Around estimated 36 million are chronically disabled that constitutes a leading cause of physical disability globally. Almost 19 million are affected by scrotal hydrocele in men, and some 17 million by lymphedema (3). The lymphedema mainly affects lower limbs and also arms, breasts and scrotum. The other LF infected persons are at risk of developing lymphedema or hydrocele.

LF is targeted for elimination by the world health assembly (World Health Assembly Resolution WHA 50.29: Elimination of LF as a

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public health problem. Fifth World Health Assembly, 5-14 May, 1997, Resolution and Decisions). The Global Programme to Eliminate Lymphatic Filariasis (GPELF) consists of two "Pillars", stopping new infections by 2020 and managing morbidity and preventing disability for persons already infected (4). Out of 73 endemic countries outlined above, Mass Drug Administration (MDA), has been already started in 62 by WHO in 2014 (5) and 45 countries are in process aiming to achieve elimination targets by WHO by 2020 (6). Significant achievement has been done in the first pillar of interruption of transmission thereby preventing new infection only 24 of 73 countries have addressed the morbidity management and disability prevention process by 2014 (6). Out of 73 countries globally endemic for the disease are mostly situated in tropical countries but found commonly in Africa and India. The distribution of the disease shows that most countries are in Africa on either side of equator. India unfortunately has bulk of the disease and bears a disproportionate burden almost hay of the global burden.

Indian Scenario

LF is still considered a major public health problem in India. Around 256 districts of about 630 million populations are being targeted in India (NVBDCP: 2017 personal communication). India alone contributes to forty percent of world burden of LF (7). While *W. bancrofti* filarial parasite accounts for 95% of the disease burden, only 5% is contributed by *Brugia malayi.* Out of 1.3 billion populations in the country, only 630 million population are at risk, over 23 million people suffer from disease and 31 million are estimated to be carriers (8). The disease is considered to be tropical debilitating disease only next to malaria (9). The total disability adjusted life years lost is nearly 2.06 million resulting in wage loss of US 811 million (10). The current data (2017) estimates round 0.38 million hydrocele and 0.84 million lymphedema in India (NVBDCP: Personal communication). In India the major chronic manifestations are lymphedema, hydrocele, elephantiasis and chyluria Tropical pulmonary eosinophilia is considered as a form of occult filariasis caused by parasite(s). The disease has a great economic impact in the country. While 2 billion USD lost per year both direct cost (out of pocket payment for care and cost to health system) and indirect cost includes lost to productivity (around 30%) and missed earning both patient and employer (NVBDCP: Personal communication).

Out of all countries in globe, India has the largest Mass Drug Administration (MDA) programme. The country targets elimination of LF by 2020. Lymphatic disease also imposes a great social burden. The disease carries a significant social stigma interfering marriage, prospects, sexual disability and decreased prospect of getting manual jobs. Frequent episodes of Acute Dermato Lymphangio Adentitis (ADLA) in cases with lymhedema and elephantiasis not only lead to painful deviating condition but also loss of wages lifelong that affect the family as well as the community. The disease is well known in ancient times, as evidenced by the script of a hydromel case in famous Konark temples of Odisha built in around 1000AD.

Historical Perspective

LF is an ancient disease and its grotesque lymphedematous limb and massive hydroceles were well known since long. India has a long history in taking efforts to control the disease through National Filaria Control Programme (NFCP). Odisha has first witnessed the LF control measures during 1950s. Several control measures were taken in many parts of the country subsequently using drug Diethylcarbamazine (DEC) and use of anti larval, anti adult entomocogical measures tools in last 4 to 5 decades. In 1980's lymphatic filarial control programme was primarily targeting towards vector control and medical impact at both clinical and immunological level. There was no concept on elimination as a public health measure. Several surgical techniques were used

to reduce limb size and drugs to address filarial sepsis caused due to infection. Until recently when paradigm shift of approach to eliminate the filarial infection and the disease occurred with advent of newer knowledge and techniques.

Clinical Disease and Infection

Both acute and chronic clinical manifestations of LF are well known since long, but the understanding about its pathogenesis, clinical progression, tools for diagnosis therapeutic strategy and approach for its elimination was not known until recently. The understanding of these filaria parasites in its biological and genomic aspect has significantly improved recently paving way for use of newer diagnostic tool to detect infection in convenient way accurately. Elegant studies now could demonstrate the location of adult parasite in human, using new tool like Ultrasonography, and Lymphoscintigraphy. The understanding as to how the parasite evades the immune attack including the role of sheath in such maneuvers.

The genetic makeup of these parasites could be revealed. The sheath of *W.bancrofti* demonstrates albumin and immunoglobulin in its surface (11). The clinical spectrum of the disease is classified in to 3 groups; microfilaria carrier, acute and chronic filarial disease. The larval form is called microfilarae that circulates in peripheral blood is considered innocuous; the adult form of parasite that remains hidden in lymphatics or in lymphnodes is responsible to initiate pathology. Atypical clinical features like lymphatic nodule due to the adult parasite seen in same human host. Lymphatic nodules were demonstrated as early as in 1980 (12, 13).

Recurrent adenolymphangitis (ADL) is considered hall mark of the disease and constitutes important risk factor for its progression to lymphedema stage (14, 15). Repeated acute episodes of ADL affects regional lymphatics followed by peripheral lymphatic sclerosis eventually towards occlusion was considered hallmark of the pathogenesis of filarial lymphedema (16). During course of the carrier stage the occurrence of adenolymphangitis associated with filarial fever is observed possibly due to host humoral response (17). These adenolymphangitis ADL episodes had a great economic impact on patients (18). Subsequently, Dreyer *et al* demonstrated Acute Dermatol-lymphangio Adenitis (ADLA) which is one of the two forms lymphangitis caused by secondary bacterial infections particularly among lymphedema patients (19) and possibly leads to progression of lymphedema to elephantiasis. Further, it was postulated that impaired lymph drainage and lack of elimination of penetrating bacteria are responsible factors for progression of lymphedema and attacks of ADLA. The broken skin of affected limb and lymph stasis encourages the bacterial growth sustaining the infection causing inflammation. The commonest organism isolated in recurrent ADLA cases is mostly streptococci that respond to penicillin and other common antibiotics.

Recent understanding on the pathogenesis of disease and its progression emerge from discoveries in identification of Wolbachia which are endosymbiotic bacteria present in these cases. These bacteria not only influence development and metabolism of parasite but also responsible for many aspect of pathogenesis of disease. The pro-inflammatory effects of cytokines released by bacteria are largely leads to post treatment reaction such as fever and more importantly for development of chronic pathology. This observations lead to another pathway of treatment of filarial infection by using tetracycline for Wolbachia. With tetracycline treatment in microfilaraemic subjects, the microfilaria (mf) cleared rapidly as opposed to those who did not receive tetracycline.

Recent Advances in Pathology

Few studies have brought more clarity to get better understanding of its pathogenesis and pathology. It is now well documented that in filarial endemic areas most of the children are infected early in life while clinical manifestation

occur during late adolescence stage or in adult. We also now recognize that lymphatic pathology in adults results from variety of factors that act on damaged lymphatics. Our recent study (20) on *W.bancrofti* infected asymptomatic young endemic children between five to eighteen years documented occurrence of subclinical lymphatic pathology shown by lymphoscintigraphy of both lower limbs.

Majority (>70%) *W.bancrofti* infected but asymptomatic children had demonstrable suclinical lymphatic pathology in their lower limbs with lymph flow observation features. All these children were treated with single dose DEC Plus Albendazole (dose as per National Programme) either annually or biannually after randomizing the group. Results clearly indicated either reversal or improvement of clinical pathology following use of single dose treatment (DEC+Albendazole) in 2 years in more than 80% children.

Post treatment reversibility and change in foot circumference was also documented in symptomatic children with lymphedema. This finding has important implication to act as a strong advocacy tool for LF programme. Finally, above study has shown that MDA is not only for interruption of transmission, but also serve as an effective tool for disability prevention and reduction of morbidity like early lymphedema in children.

Clinical Features: Cause of Disability

Once the filarial infection is established, the clinical course of the disease passes through various stages and time period may progress to end-up with chronic stage that causes serious disability. Although the ADL episodes accompanying mild edema distally in limb resolve in 3-7 days, these often tend to recur, where edema becomes persistent and non pitting with stasis of lymphatic fluid at interstitial tissue spaces in edematous site in limb. With recurrence of adenolymphagitis, edema progress to full form of irreversible lymphedema due to gross changes in lymphatic architecture, lymph dysfunction and lymph stasis. The affected area usually in extremities or sometime in scrotum becomes potential sites of inflammation in presence of precipitating factor.

Once lymphatic drainage to the limb or scrotum in male get obstructed in late stage of lymphedema, the affected limb or scrotum favor entry of bacteria, causing acute inflammation of the affected skin, draining lymph vessels and regional lymphnode, called ADLA. In unhygienic situation, the organism gain entry through inter digital spaces site of injury, eczema or cracks in the feet. Higher grades of lymphedema sometimes affected by fungal infection aggravated in rainy season, when feet are soaked with water. Repeated attacks of ADLA further damage the lymph drainage and lymphedema progress to elephantiasis, during attack of ADLA, the limb/scrotum becomes extremely painful, warm, red, swollen, and tender with systematic reaction like higher fever.

A paradigm shift is reflected in our knowledge as to how the attack of ADL or ADLA occurs in Filariasis. While the early asymptomatic mf carrier stage, exhibits ADL due to periodic release of toxic material from parasite. Late stages of lymphedema clearly established the role of secondary bacterial infection that invades the already damaged lymphatics. Above, observation paved way to the concept of current management of ADLA associated with LF.

Advancements in the Diagnosis of LF

Newer diagnosis have not only made the process convenient during field collection and processing of blood specimens in daytime, but also yielded most accurate assessment of detection of filarial infection by antigen detection test (ICT) and mapping of the disease to identify endemic areas. The OG4C3 antigen test assay allowed testing of large numbers of specimens in laboratory. To detect brugia infection, brugia rapid assay is used based on the detection of antibody. Use of color droppler ultrasonography, the adult parasite can be

detected in non-invasive manner from hidden locations, usually in axilla, inguinal region or afferent lymph channels to draining lymphnode. The array of lymphatic architecture and lymph flow pattern can be studied through lymphoscintigraphy that made a paradigm shift to our knowledge.

Newer Pharmacotherapeutics for LF Elimination

Dramatic change in concept has been witnessed in last decade that added knowledge on therapeutics from 12 days individual treatment to a single dose MDA to achieve elimination of LF. This has paved the way to formulate a global program for elimination of Filariasis. DEC has been the drug of choice and was given for 12 days for treatment of Filariasis to suppress mf for long period in a slow but sustained manner. Studies clearly demonstrated that single dose of DEC can achieve mf suppression equally as that of 12 days regimen. The observation of effect of 6mg/kg dose of DEC given in single dose followed the study that evaluated invermectin when administered in single dose and compared with DEC as a powerful microfilariacide (21). This useful observation had paved way for genesis of MDA strategy.

A community based trial undertaken to evaluate effectiveness and side reaction score of alternative doses of DEC used as MDA with low doses 100 mg, 200 mg or 300 mg dose given uniformly in all age groups in 3 different matched population groups. The result revealed that low dose of DEC (100 mg) is comparable to enhanced doses of DEC in of mf suppression with significantly less side reaction. It can be believed that this finding will have important impact on improving compliance, ease of drug delivery and in decreasing drug requirement if low dose DEC (100 mg) is used to all age groups above 2 years. Currently programme uses 300 mg of DEC Plus Albendazole 400 mg given annually. Further the study addressing doubling the dose of Albendazole to 800 mg given bianually has significantly prolonged mf suppression along with reduction of mf density in 2 year study (22). Beside this regimen has exhibited clearance of the adult parasite as well as antigenemia.

The recent findings on trials with Doxycycline given in doses of 200 mg daily for 6 weeks has shown promise as powerful filariasis effect with its anti-inflammatory action which are independent of anti-filarial activity and can reduce lymphedema. Some countries have also attempted to use DEC fortified salt. Summarizing these results it is now clear that there are several options open for use as drug regimen for MDA to achieve better compliance, effective mf and adult worm clearance and the possibility of reducing the number of rounds the MDA programme has to continue to achieve desired result.

Management of ADLA

With better understanding of pathogenesis of acute attack of ADLA, it is now possible to formulate simple strategies for management of simple acute attack (19). ADLA can be easily treated and further attacks are prevented. Bed rest and paracetamol are enough in mild cases for treatment. Local precipitating factors to be assessed and treated appropriately like injury and associated fungal or bacterial infection, Moderate to severe ADLA may require oral or parenteral antibiotic along with analgesics or antipyretics drug. Community awareness about ADLA and its prevention on has been initiated in many endemic areas to curtail the episode and improve quality of life.

Management of Lymphedema

With new knowledge on pathogenesis of LF, the management of filarial lymphedema now relies on limb washing, foot care, physiotherapy and precautions to prevent acute attack.

Current Programme for Elimination of LF

New insights on the disease, the parasite diagnostic tools and available chemotherapy

options have been used to initiate Global programme for elimination of LF, in year 2000. The programme was launched first to eliminate LF as a public health problem by 2020. Besides the two pillars of GPELF the vector control and integrated vector management play supplementary role are already illustrated. MDA strategy is the basis of interruption of transmission is based on the earlier studies that can suppress mf for long period, thereby annual single dose of MDA given in 5 to 6 rounds can reduce mf level to a point where no new infection can occur. The addition of Albendazole to either DEC or Ivermectin enhances the effect of long term mf suppression that forms the basis for MDA.

For future, based on recent ongoing clinical trials under taken in the globe including India indicates that triple drug therapy, i.e. annual single dose of MDA consisting of DEC, Albendazole and Ivermectin can not only achieve prolonged mf suppression but also sustain the effect for long period, with clearance of adult parasite, Thus this provides opportunity of reducing the number of rounds to achieve interruption of transmission. This regimen can be applied to areas where either MDA is not achieved yet or areas where it is not initiated.

These new chemotherapy trials can facilitate effective MDA application since these can be distributed by community health volunteers and can be given once a year. The other advantage is that these drugs are already in clinical practice and now management of side effects can be easily carried out.

The filarial elimination programme has several potential benefits apart from addressing filarial elimination. Since these drugs are very effective in treatment of soil transmitted helminthes, the benefits like decrease in intestinal helminthes burden and consequent decrease in anemia and increase in nutrition & growth can be achieved. Additional benefits of treatment of scabies by Ivermectin (21) together that constitute what is called –benefits beyond filariasis effect.

The Indian programme to eliminate LF is considered as largest such programme in the world. It requires the massive distribution of more than one billion DEC and Alb dosage every year. Nearly 2.5 million workers are required every year for their distribution. Thus it is often said the success of global programme will be more pronounced as per success of Indian programme.

Current Global LFE Programme

Global programme for elimination of lymphatic filariasis (GPELF) was launched in year 2000. MDA scaled up dramatically globally after launch of GPELF and this considered is one of the most rapidly expanding global health programme in history of public health. During 1st 10 years after it is launched, MDA increased from 3 million in 12 countries in year 2000 to 466 million 53 countries in 2010. Between 2000 to 2014 cumulative total of 5.62 million treatments were delivered to over 1 billion people at least once. Out of 73 endemic countries, all implementation units (IU) of 23 countries could not start MDA, but 21 had achieved 100% coverage, and 18 states transitioned to post MDA surveillance and no longer require MDA, Effective water, sanitation and hygiene (WASH) campaigns, environmental sanitation and house construction significantly eliminated filariasis in china and Korea. Alternative treatment strategies and intervention approaches like MDA at high coverage (100% coverage) twice yearly treatment, different combination of drug (like Annual single dose combination MDA regimen (DEC+Albenazole+Ivermectin) and supplementary vector control measure could accelerate the interruption of transmission.

WHO predicted that MDA with DEC+Albendazole will require coverage of 70% or more in transmission zones to achieve LFE by 2020? Addition of Ivermectin to existing MDA regimen may improve mf clearance and provide a long lasting effect and require less rounds of MDA. Yet another new therapeutic option has been shown that 6 week course of

Doxycycline 200 mg daily dose for six weeks may help in reverting or halting the early stage lymphedema, regardless of the presence of an active infection.

While the first part of GPELF goal (MDA) for interruption transmission is mostly realized, through sequential mapping, MDA, post MDA surveillance and verification in many endemic areas, efforts are on the way to analyze country situation on MMDP, developing plan and providing access to a minimum package of care to affected cases with chronic morbidities like lymphedema and hydrocele cases with 100% geographical coverage. Each endemic country has to pass the Transmission assessment surveys (TAS) undertaken by WHO in 3 phases in 4 years after stoppage of MDA for verification and certification by WHO Each country can identify the area where LFE can be integrated to prevention of other conditions of NTDS soil transmitted helminthes, leprosy, diabetes foot care and malaria to make it more robust & economical.

Elimination of LF as a public health problem: as desired is defined as reduction in measurable prevalence of infection in endemic areas below a target threshold (<1% mf & Ag) at which further transmission is considered unlikely. TAS in 3 stages will assess above to ensure sustainability in 100% coverage implementation.

Now What does the Future Hold for LF?

Whether the global programme will be finally completely successful? We can envisage world free of LF, and its morbidities however several challenges have to be overcome and opportunity utilized to achieve ultimate goal. All over the tropical world several NTDS occur in the same endemic area, e.g. in India there are areas with at least 3 NTDS are present. LF, STH and Visceral Leishmaniasis (VL) in parts of India or more diseases like Hansen's disease may co-exist in the same region. Treating the diseases where they co-exist remains a challenge in terms of chemotherapeutic approaches, drug delivery and monitoring and evaluation. However, source of the beyond filariasis effect of the drug such as IVM and Alb as listed holds promise for integrated approaches for treatment. Similarly opportunity exists for tackling multiple diseases in area of morbidity management, vector control and preventive chemotherapy. Availability of several partnerships between the WHO, MoH, NGO and many other donors also provide important opportunities for developing integrated approach. However, several challenges for integration still remain. These include ensuring high compliance, management of drug interaction and identifying possible drug resistance.

Apart from integrated approach with existing wide network for drug distribution the success of elimination also depends on simultaneous social and economic development that includes availability of clean water and improved sanitation. All these efforts need to be strengthened with adequate monitoring and evaluation and strong IEC effort. Ultimately, despite the advances in various fields the success of the programme will depend on strong political and administrative support and heightened advocacy and social mobilization to ensure complete participation by the communities. When these occur we can promise that young citizens of our country and land will be free of filariasis.

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