

INTRODUCTION

Infections with human filarial nematodes affect 170 million people world wide out of which more than 150 million people are from the tropics. Eight filarial species infect humans; of the, four-*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa* are responsible for most serious filarial infections.

Lymphatic filariasis (LF) is a major cause of clinical morbidity, disfigurement and disability in endemic areas, leading to significant economic and psychosocial impact. It is the world's second leading cause of permanent long-term disability (after mental illness) and thought to be only next to malaria among the tropical debilitating diseases. LF is caused by nematodes that inhabit the lymphatic and subcutaneous tissue, transmitted by mosquito vectors and humans are definitive hosts. Three filarial species cause LF: *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. *W.bancrofti* is responsible for almost 90% of the disease burden in the tropical countries while the remainder is largely due to *B.malayi*. Approximately 120 million people in 83 endemic countries worldwide are estimated to be infected with filarial parasites. Estimates suggest that more than 40 million infected individuals are seriously incapacitated and disfigured by this neglected tropical disease. Overall, nearly two-thirds of individuals infected with LF are in Asia. It is still a public health problem in India and is endemic in 17 states and 6 union territories. India accounts for 40% of the world disease burden. About 31 million people are estimated to be the carriers of microfilaria and over 23 million suffer from filarial disease manifestations in India. A study from India has estimated that more than \$ 840 million is lost each year due to treatment costs and missed working days. Another study from India reported that patients with chronic filariasis lose around 29 days of work per year due to complications of infection.

PATHOGENESIS

The pathogenesis depends on various factors like host immune response to adult worms, super added bacterial infection and agent factors like endosymbiotic bacteria *Wolbachia*. When the adult worm dies either with drugs or naturally at the end of their life spans, an inflammatory reaction including granulomas, macrophages and eosinophils develops. At this time release of *Wolbachia* add to the inflammatory response. The filarial degeneration products and *Wolbachia* results in an increase in Th_1 , Th_2 and Th_{17} numbers leading to

the release of inflammatory cytokines like TNF, IL-1 β , and IL-6. These contribute to lymphangiectasia which has already started during the period when adult worms were alive and lymphangiogenesis through vascular endothelial growth factors (VEGF-A, VEGF-C, VEGFR-3). These deformed lymphatic vessels are less efficient in transporting lymph from periphery especially legs leading to stasis of lymph which predisposes to secondary bacterial infections, specially streptococci leading to acute dermato-lymphangio-adenitis (ADLA) which leads to lymphedema if not properly managed. Recurrent attacks of ADLA results in irreversible skin and dermal changes of elephantiasis.

DISEASE SPECTRUM OF LYMPHATIC FILARIASIS

The disease profile of LF ranges from the initial phase of asymptomatic microfilaremia to later stages of acute and chronic clinical manifestation. Estimates suggest that only about one-third of infected individuals in endemic areas will develop clinical manifestations and rest are asymptomatic (sub clinical). Proper understanding and the clinical manifestations will help in managing the cases.

Asymptomatic Microfilaremia

Infected patients who have a down regulated immune system towards filarial antigens demonstrate high levels of microfilariae in their blood without any overt clinical manifestations. Even at this stage there is hidden damage to their lymphatics like dilation and tortuosity which are demonstrable by ultrasound (US) examination and lymphangio- scintigraphy (LSG). These abnormalities are usually irreversible, even after treatment.

ACUTE MANIFESTATIONS**Acute Dermato- Lymphangio- Adenitis (ADLA)**

Attacks of ADLA are characterised by localized pain and tenderness, lymphadenitis and/or lymphangitis and / or cellulitis and local warmth, with (mostly 97% cases) or without systemic manifestations of fever, nausea and vomiting. Secondary infections due to bacteria like Group A streptococcus are responsible for these acute episodes and lesions favouring entry of bacteria can be demonstrated in the affected limbs. If attacks of ADLA are not properly treated or prevented, recurrent attacks are responsible for persistence and progression of lymphedema leading to elephantiasis.

Acute Filarial Lymphangitis

It is caused by spontaneous or drug induced (Diethyl

carbamazine-DEC) destruction of adult worms. Small tender nodules develop at the site of death of worm either in the scrotum or along the lymphatics. The inflammation is retrograde progressing from the lymph node to the periphery with the lymphatics standing out as inflamed tender cords. There is no fever, toxemia or evidence of secondary bacterial infection.

Acute Epididymo - Orchitis and Funiculitis

Inflammation of structures in the scrotal sac may result in acute epididymo-orchitis or funiculitis in bancroftian filariasis. This is manifested by severe pain, tenderness and swelling of scrotum, usually with fever and rigor. The testes, epididymis or the spermatic cord may become swollen and extremely tender like ADLA. These attacks are also precipitated by bacterial infections.

Tropical Pulmonary Eosinophilia

This is caused by an immune hyperresponsiveness to microfilariae trapped in the lungs and is characterised by nocturnal cough, dyspnea, marked peripheral blood eosinophilia (>3000 cell/cumm), diffuse reticulonodular infiltrates in radiological examination of chest and primary restrictive defects with mild obstruction in pulmonary function test (PFT).

Filarial Fever

Filarial fever is characterised by acute, self limited episodes of fever, often in the absence of lymphangitis or lymphadenopathy.

CHRONIC MANIFESTATIONS

Lymphedema and Elephantiasis

One of the most common chronic manifestations of LF is lymphedema of the extremities which on progression leads to elephantiasis. Even though lower limbs are frequently affected, upper limbs, male genitalia and breasts in females may also be affected rarely. Recurrent ADLA is responsible for the progression of lymphedema to elephantiasis.

Genitourinary Lesions

Hydrocele is a common chronic manifestation of bancroftian filariasis. Other genitourinary manifestations are chylocele, chylohematocele, lymphocele, hematuria, chyluria and proteinuria.

DIAGNOSIS

A diagnosis of LF should be considered in any patient with an appropriate exposure history who presents with characteristic signs and symptoms or unexplained eosinophilia. Definitive diagnosis can be made by detection of circulating filarial antigen (For *W.bancrofti* infection only), demonstration of microfilariae or filarial DNA in the blood or of adult worms in the lymphatics. Rarely, microfilariae and/or adult worms are identified incidentally in tissue biopsies or cytological specimens.

Circulating Antigen detection

Circulating filarial antigen (CFA) assays have been developed for diagnosis of *W.bancrofti* infections but are not yet available for Brugian filariasis. This is regarded as

“gold standard” by World Health Organisation (WHO) for diagnosis of LF. These tests detect antigens released by adult filarial worms and may be positive in cryptic (amicrofilaremic) infection. In addition antigen level remains stable during the day and night, so these tests can be performed at any time. Two CFA tests are commercially available for specific detection of *W.bancrofti*: an Og4C3 monoclonal antibody - based enzyme - linked immunosorbent assay (ELISA) which gives a quantitative result that correlate with adult worm burden and a rapid format immuno chromatographic technique (ICT), which gives only qualitative results. In comparison with microfilarial detection in blood, CFA has been found to be 94% to 100% sensitive and 90% to 100% specific. False positive *W.bancrofti* antigen test results are common in patients with large numbers of circulating loa loa microfilariae. In addition, a negative test exclude filarial infection as a cause of chronic pathology since filarial antigens eventually become undetectable in treated or “burned out” infection, even in the settings of lymphatic damage. Although the quantitative Og4C3 ELISA may be of some use in following patients after treatment since antigen levels typically decline with treatment, it remains unclear whether a persistently positive antigen tests should prompt additional therapy.

Microfilarial detection

Microfilariae can be detected in blood, urine or hydrocele fluid through direct microscopy. Examination of blood smears for microfilariae should be performed in all individuals in whom the diagnosis of filariasis is suspected, if CFA tests are not available or Brugian filariasis is a consideration based on exposure history. The timing of the blood collection is critical and should be based on the periodicity (between 10 pm and 2 am) of the microfilariae in the endemic region involved. Concentration technique (e.g. Nuclepore filtration and Knott's concentration) are more sensitive as they facilitate examination of larger quantities of blood. DEC provocation test is used to facilitate day time detection of microfilariae.

Imaging Studies

In cases of suspected LF, examination of the scrotum, lymph nodes, or the breasts (in females) by means of high frequency ultrasound in conjunction with Doppler techniques may result in the identification of motile adult worms within dilated lymphatics. Live adult worms have a distinctive pattern of continuous motion within the lymphatic vessels described as “filarial dance sign”. Radionuclide lymphoscintigraphy is a useful tool for assessing the extent of lymphatic damage in both overt and subclinical microfilaremic persons.

DNA based Diagnosis

DNA - based techniques like polymerase chain reaction (PCR), though not as sensitive as CFA assays, are more specific. PCR amplification of the glutathione peroxidase gene helps in diagnosis of LF and restriction fragment length polymorphism (RFLP) enables differentiation of species.

Antifilarial antibody test

Serological tests for filarial antibodies that detect elevated levels of IgG and IgG4 are available. The majority of these assays are based on crude antigen mixtures; therefore, they don't differentiate between the various types of filarial infections and often cross react with antigens from other helminths. Further more, since these tests can't distinguish between active infection and past infection or exposure, they are useful primarily in detecting infection in travellers from non endemic areas and have little predictive value in long-term residents of endemic areas. Although a negative test can help exclude recent infection, patients with chronic manifestations of lymphatic filariasis can become antibody negative over time.

Several assays based on recombinant antigen appears to have enhanced specificity. These include two rapid IgG4 antibody detection tests: BRUGIA rapid, which is specific for Brugia antigen BmR1 and PanLF Rapid, which combines Brugia Rapid with a test for BmSXP that detects infection with both Brugia species and *W.bancrofti*. An IgG4 assay specific for the recombinant antigen Wb123 appears to be a sensitive and specific marker of early infection with *W.bancrofti* and is in development as a rapid diagnostic test.

Treatment

The approach to treatment of LF requires an understanding of antimicrobial agent mechanisms as well as attention to the possibility of coinfection. The clinical approach is described below, followed by a discussion of data related to individual antimicrobial agents.

Clinical Approach to Therapy

Orally administered diethyl carbamazine (DEC) remains the drug of choice for treatment of active LF (defined by microfilaremia, antigen positivity or adult worms on ultrasound). It is contraindicated in patients coinfecting with onchocerciasis and must be used with caution in patients with loiasis, since severe adverse events can occur in individuals with high microfilarial loads.

Monoinfection

Patients with LF (in the absence of onchocerciasis or loiasis) should receive treatment with DEC (6 mg/kg daily for 12 days), regardless of whether clinical symptoms or microfilaremia are present. Asymptomatic patients who have microfilaremia have some degree of subclinical disease (hematuria, proteinuria, lymphatic damage) also need early treatment to prevent further lymphatic damage. Reversal of early lymphatic damage has been observed following DEC treatment. Evidences suggest that addition of doxycycline (200 mg/day for four to six weeks) also reduces pathology in mild to moderate disease. Treatment is generally warranted even in the setting of advanced disease who have evidence of active infection or to kill any remaining adult parasites although clinical improvement may be limited.

Concomitant infection

DEC is contraindicated in patients coinfecting with onchocerciasis and/or patients with loiasis who have high

microfilarial loads due to possibility of severe adverse events.

Onchocerciasis

DEC is contraindicated in these patients due to potential for severe adverse events related to killing of microfilariae in the eye and /or skin. Therefore, ivermectin (150 mcg/kg single dose) should be administered to clear *O. volvulus* microfilariae in the skin and eye prior to standard treatment of LF with DEC (preferably one month). Alternatively, doxycycline (200 mg orally once daily for 4 to 6 weeks) followed by ivermectin (150 mcg/kg orally single dose) can be used to treat both infection, although the relative efficacy of this regimen compared with standard therapy for the treatment of LF is not known.

Loiasis

For patients with LF who are coinfecting with loa loa but have less than 2500 loa loa mf/mL of blood, DEC therapy using the standard regimen for loiasis (8 to 10 mg/kg/day for 21 days) should be administered. For patients with higher levels of loa loa microfilaremia, doxycycline (200mg orally, once daily for 4 - 6 weeks) or albendazole (200 to 400 mg twice daily for 21 days in who can not take doxycycline) are the drugs having no effect on loa loa microfilariae, are the treatment of choices for LF. Heavy loa loa microfilaremia (>8000 mf/mL) can be treated initially with apheresis to remove the microfilariae and with glucocorticoids (40-60 mg of prednisone/day) followed by doses of DEC (0.5 mg/kg/day). If antifilarial treatment has no adverse effects, the prednisone dose can be rapidly tapered and the dose of DEC gradually increased to 8-10 mg/kg per day.

Antimicrobial Agents

Selection of therapy for treatment of LF requires an understanding of the macrofilaricidal and microfilaricidal activity of therapeutic agents. The epidemiology of other filarial diseases is also important; in regions where loiasis and onchocerciasis may coexist with LF, additional consideration is important for minimizing the likelihood of adverse effects.

Diethyl carbamazine

DEC, is a potent microfilaricidal and macrofilaricidal agent with activity against *W. bancrofti*, *B. malayi* and *B. timori*. Estimates suggest that DEC kills approximately 50% of adult worms and its effect on adult worms in turn decreases the microfilarial burden. It significantly lowers microfilariae levels even in single annual doses of 6 mg/kg body weight which makes it a perfect antimicrobial agent in the campaign to eliminate LF transmission through mass drug administration (MDA). It is also treatment of choice with loa loa coinfection. Direct adverse effects of DEC are rare; most of the side effects like rash, fever, headache, anorexia, nausea, cough, myalgia and arthralgia are likely attributable to the host response following death of microfilariae (systemic immune reactions) and damage to adult worms (local reaction). These adverse effects lasts for 24 to 48 hours and management is symptomatic (antipyretics and/or anti inflammatory agents). Since

post DEC reactions are more severe in onchocerciasis and loiasis, evaluation for these coinfections should be persuaded prior to administering DEC. DEC should be avoided in pregnancy. It is not excreted in breast milk and is considered safe during lactation.

Ivermectin

Ivermectin has microfilaricidal activity but does not have significant macrofilaricidal activity. Therefore, the reduction in microfilaremia is not sustained without repeat dosing. The clinical benefits of ivermectin are uncertain as it lacks activity against adult worms, which play important role in pathogenesis of lymphangitis and lymphedema. It may have some role in reducing fertility of worms. It is as effective as DEC in reducing microfilaremia due to Bancroftian filariasis. A single dose has been shown to reduce microfilaremia by approximately 90 percent even one year after treatment. It is the drug of choice for onchocerciasis and should be used as part of the regimen to patients with concomitant LF and onchocerciasis but is contraindicated in patients with loiasis and high levels of loa loa microfilariae in the blood due to risk of post treatment encephalopathy. It is contraindicated during pregnancy and lactation. Adverse effects are similar to DEC but slower due to slower clearance of parasitaemia.

Albendazole

Albendazole has no microfilaricidal activity but leads to slow decline in microfilaremia due to macrofilaricidal activity against the adult worms (400mg twice daily orally for 14 to 21 days). Consequently, side effects due to rapid killing of microfilariae are not seen and albendazole can be used in patients with concomitant loiasis and onchocerciasis. A single dose of albendazole 400 mg greatly accelerates the microfilaricidal action of DEC. Therefore, the strategy of combining single annual dose of DEC 6 mg/kg body weight with albendazole 400 mg is appropriate for eliminating LF in India. Studies have showed enhanced suppression of microfilaremia with albendazole and ivermectin as compared to ivermectin alone. Severe scrotal reaction might be induced by death of adult worms inside the scrotal lymphatics.

Doxycycline

A promising alternative approach to attack worm directly is to focus treatment against Wolbachia that is present in microfilariae and adult worms of *W. bancrofti* and both *Brugia* species. By destroying Wolbachia it reduces the plasma levels of VEGFs, thus reduce lymphatic dilation. It has both microfilaricidal and macrofilaricidal activity. It has been shown that, doxycycline in a dose of 200 mg/day for 8 weeks (even 4 to 6 week) result in a sustained decrease in blood microfilariae level as does DEC / albendazole used daily for 7 days. Addition of albendazole may enhance macrofilarial clearance by doxycycline. There is also convincing evidence that doxycycline treatment alone or in combination with DEC (3 weeks doxycycline) reduce clinical pathology including lymph vessel dilation and hydrocele in affected individuals. It is most effective when combined with DEC-albendazole or ivermectin with the added advantage of doxycycline pretreatment markedly

reducing the adverse events following DEC-albendazole administration. Doxycycline is contraindicated in pregnancy, lactation and children less than 8 years of age.

The treatment of LF involves not only antifilarial drug therapy but it also encompasses the management of asymptomatic carriers, treatment and prevention of ADLA, management of lymphedema/elephantiasis and patient counselling/education.

Asymptomatic carriers

DEC is the drug of choice for treatment of asymptomatic carriers at a dose of 6 mg/kg/day in divided doses for 12 days, preferably combined with single dose of albendazole or ivermectin. Prior treatment with doxycycline 200mg/day for 6 weeks before DEC-albendazole administration gives better results with less adverse drug reactions.

Acute Dermato-Lymphangio-Adenitis

Early, aggressive management and prevention of episodes of ADLA is the key to prevent the progression towards elephantiasis. Bedrest and symptomatic treatment with simple drugs like paracetamol are enough in mild cases. Any local precipitating factors like injury and bacterial or fungal infection should be treated with local antibiotics or antifungal ointments. Moderate or severe attacks of ADLA require rest, proper hydration, oral or parenteral antibiotics depending on the general condition of the patient, together with antipyretics / analgesic drug and cold compresses to alleviate pain. The preferred commonly used antibiotics are penicillin, tetracycline, ampicillin, amoxicillin or cotrimoxazole in adequate doses and duration till the infection subsides. Culture and sensitivity examination of swabs from the entry lesions may help in selecting the appropriate antibiotic in severe cases. Systemic antifungal therapy is rarely required since the fungal infections of the skin act as only entry points for the bacteria and fungi themselves do not cause ADLA.

Prevention of Acute Dermato-Lymphangio-Adenitis

Presently there is a simple, practicable, effective, cheap and sustainable method available for prevention of recurrent attacks of ADLA. Recent studies have revealed that this can be achieved by proper "local hygiene" of the affected limbs; need to be carried out regularly. Foot-care aimed at prevention of secondary bacterial or fungal infections have become the mainstay for disability alleviation or prevention in Global Programme for Elimination of Lymphatic Filariasis (GPELF). Patients, community health workers and also providers of "home care" should be trained in this foot-hygiene programme (Table 1).

In patients with advanced stages of lymphedema, proper local care of the limb is not always possible due to deep skin folds or warty projections. If such patients have recurrent ADLA attacks, long-term antibiotic therapy using oral penicillin or long acting benzathine penicillin 1.2 MU, deep IM every 3 weeks is indicated. Recent evidences have shown that antifilarial drugs like DEC have no role either in the treatment or prevention of the acute ADLA attacks occurring in case of lymphedema which are caused by bacterial infections. In endemic areas, regular foot care

Table 1: Prevention of Acute Dermato- Lymphangio-Adenitis

- Washing of the affected area, especially the webs of toes and deep skin folds, with soap and water twice a day
- Thorough gentle drying after washing
- Massage with simple emollients like coconut oil
- Applying antibiotic ointments to any local infection / injury
- Treatment of any local fungal infection with local antifungal ointments
- Nails to be kept clean and trimmed
- Elevation of affected limb at night / during rest
- Gentle exercise of affected limb regularly
- Regular use of proper foot wear

Table 2: Treatment and prevention of Lymphedema

- Regular manual light massage of the limb with an emollient with a gentle upward milking pattern to stimulate the lymph vessels and to promote flow of lymph towards larger patent vessels
- Using crepe bandage, elasto crepe bandage or tailor made stocking while ambulant, ideally after manual massage
- Intermittent pneumatic compression of the affected limb using single or multicell jackets
- Heat therapy using either wet heat or hot ovens
- Interferential therapy using medium frequency currents helps in relieving painful muscle spasms
- Limb elevation in night after removing the compression bandage
- Regular exercise of the affected limb
- Surgical procedures: see text.

should be encouraged from early childhood age, as LF is first acquired mostly in childhood leading to irreversible lymphatic damage.

Treatment and prevention of Lymphedema

Once lymphedema is established there is no permanent cure and treatment with DEC does not seem to reverse the existing lymphatic damage. All the measures mentioned in Table 1 for preventing ADLA, play important role in decreasing lymphedema progression. The following treatment modalities offer relief and help to prevent further progression of the lymphedema are described in Table 2. Oral and tropical benzopyrones and flavonoids are suggested for the treatment of lymphedema. These drugs are thought to reduce high protein oedema by stimulating macrophages to remove the proteins from the tissues when administered for long periods. Further randomised controlled trials are required to establish this fact. Chyluria may be associated with secondary nutritional deficiency. In such cases, low fat, high-protein diet supplemented with medium-chain triglycerides can be helpful

Surgery is usually the last option for treating lymphedema / elephantiasis but the long term benefit is still unclear. There are various surgical options available to offer relief of lymphedema, like lymph nodo-venous shunts, omentoplasty, and lymphatico-venous anastomosis to enhance lymphatic drainage in limb. Excisional surgery of the affected skin and subcutaneous tissue, closed by skin flap or graft is usually complicated by lymphorrhoea, haemorrhage and lymphangitis. Hydrocele and lymphedema of external genitalia require surgical management when response to medical therapy is incomplete.

Global Programme to Eliminate Lymphatic Filariasis (GPELF)

The World Health assembly called for LF to be eliminated as a public health problem in 1997. Whose response included the launch of GPELF in 2000. An important tool for elimination is MDA with albendazole combined with either ivermectin or DEC, for which the minimum effective coverage of the total population is considered to be 65%

and has been targeted for elimination by 2020. India is a part to the GPELF and through its National Filaria Control Programme (NFCP) has started a campaign of MDA of single annual dose of DEC or DEC - Albendazole to interrupt transmission of the disease.

CONCLUSION

LF is still a public health problem in India harbouring 40% of world disease burden. The pathogenesis and clinical progression of filarial disease is likely influenced by a number of factors, including the host immune response to adult worms, release of endosymbiotic bacteria wolbachia and the number of secondary bacterial infection. Definitive diagnosis of LF can be made by detection of CFA, demonstration of microfilaria or filarial DNA in blood or of adult worm in lymphatics. Patients with LF (in absence of onchocerciasis or loiasis) should receive treatment with DEC. The addition of doxycycline is also appropriate. Patients with concomitant infection due to LF and onchocerciasis should undergo treatment of onchocerciasis first either with ivermectin alone followed by standard treatment for LF or alternatively doxycycline followed by ivermectin in proper dose and duration. The approach to patients with concomitant infection due to LF and loiasis depends upon the level of circulating loa loa microfilaremia. Treatment of ADLA comprises of bed rest, antipyretics / analgesics, local application of antibacterial / antifungal ointments and oral or parenteral appropriate antibiotics in proper dose and duration. Prevention of recurrent attacks of ADLA can be achieved by maintaining proper local hygiene of the affected limbs following foot care programme judiciously. Lymphedema can be managed and its progression can be prevented by aggressive treatment of secondary infections, proper local hygiene and different manoeuvres to stimulate the lymph vessels and to promote flow of lymph towards larger patent vessels. Various surgical options are available to provide relief from advanced lymphedema / elephantiasis as a last resort. Hydrocele of the scrotum and lymphedema of external genitalia are amenable to surgery. The WHO's

initiative of GPELF to eliminate this parasite infection through MDA is one of the most economical and effective disease control strategies undertaken so far in public health programmes.

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