

Clinical and Pathological Aspects of Filarial Lymphedema and Its Management

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Abstract: Lymphatic filariasis, transmitted by mosquitoes is the commonest cause of lymphedema in endemic countries. Among 120 million infected people in 83 countries, up to 16 million have lymphedema. Microfilariae ingested by mosquitoes grow into infective larvae. These larvae entering humans after infected mosquito bites grow in the lymphatics to adult worms that cause damage to lymphatics resulting in dilatation of lymph vessels. This earliest pathology is demonstrated in adults as well as in children, by ultrasonography, lymphoscintigraphy and histopathology studies. Once established, this damage was thought to be irreversible. This lymphatic damage predisposes to bacterial infection that causes recurrent acute attacks of dermato-lymphangio-adenitis in the affected limbs. Bacteria, mainly streptococci gain entry into the lymphatics through 'entry lesions' in skin, like interdigital fungal infections, injuries, eczema or similar causes that disrupt integrity of skin. Attacks of dermato-lymphangio-adenitis aggravates lymphatic damage causing lymphedema, which gets worse with repeated acute attacks. Elephantiasis is a late manifestation of lymphatic filariasis, which apart from limbs may involve genitalia or breasts. Lymphedema management includes use of antifilarial drugs in early stages, treatment and prevention of acute attacks through 'limb-hygiene', antibiotics and antifungals where indicated, and physical measures to reduce the swelling. In selected cases surgery is helpful.

Key words: Lymphatic filariasis, Lymphatic dilatation, Lymphedema, Elephantiasis, Dermato-lymphangio-adenitis, Entry lesions, Limb-hygiene

INTRODUCTION

Lymphatic filariasis (LF) is a vector-borne disease of the tropical and subtropical countries due to infection by filarial worms, which invade the lymphatics of humans initiating pathological changes leading to later filarial disease manifestations. The nematode species that cause LF include mostly *Wuchereria bancrofti* (90%), to a lesser extent *Brugia malayi* (10%), and *Brugia timori* to a very small extent. The genera of mosquitoes transmitting these parasites include *Culex*, *Anopheles*, *Aedes* or *Mansonia*. Globally, around 120 million people in 83 countries are affected by this malady, which is ranked as the second most common cause of physical disability. Among the debilitating vector-borne tropical diseases LF is next only to malaria [1].

In endemic countries LF is the commonest cause of lymphedema, which mostly affects the lower limbs, sometimes the arms, less commonly male genitalia, and rarely breasts and genital region in females. It is estimated that up to 16 million people in endemic countries have filarial lymphedema [2]. Several studies have documented the physical, social, psychological, sexual, and economical problems resulting not only

from the deformities caused by LF but also from the acute febrile episodes associated with this disease [3-5].

A number of new advances in understanding the pathogenesis of this disease, the biology of the parasite, and development of newer methods for diagnosis and better knowledge of the action of safe and effective chemotherapeutic agents have all contributed to the notion that LF can be eliminated from endemic countries. Identified as one among only 6 potentially eradicable diseases, LF is now targeted for global elimination as a public health problem, based on the World Health Assembly resolution in the year 1997 [6,7]. This Global Programme for Elimination of LF (GPELF) launched in 2000 has 2 arms consisting of (a) interruption of transmission by annual mass drug administration (MDA) to prevent LF infection in the communities and (b) alleviation of disability in those who already have the disease [8]. In this article the pathogenesis and clinical presentation of lymphedema due to filariasis and its management are discussed. The importance of recognizing LF as an infection occurring in childhood and its prevention are also stressed.

PATHOGENESIS

The infective larvae (L3) deposited on the skin of the human host penetrate the skin and enter the lymphatics where they

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develop into adult worms. In bancroftian infections, the preferred site where the adult parasites live is the scrotal lymphatics in the adult men or even in boys after puberty, made out on ultrasonography by the presence of 'filarial dance sign' (FDS) [9,10]. Other common locations described in women and children are larger lymph vessels and lymph nodes draining to lower and upper limbs [11,12]. In brugian filariasis also adult worms were detected by Doppler sonography in the lymphatics of the inguinal and axillary regions in children [13]. The adult parasites live in these sites for 6-8 yr or more and are responsible for initiating the early pathology in LF.

It is now well known that the earliest structural change in LF is the dilation of lymph vessels where the adult worms live. This has been demonstrated in subjects who are clinically asymptomatic except for presence of microfilariae (mf) in blood, by ultrasound examination of the lymphatics of the spermatic cord; lymphoscintigraphy of the limbs and by direct examination of lymph vessels resected by surgery [9,14]. Dilatation of the lymph vessels has been demonstrated by lymphoscintigraphy even in children with brugian filarial infection [15]. It is believed that this damage to lymph vessels is caused by the adult parasites through mediators produced by them, which cause vessel dilatation or inhibit contractility [16]. In course of time this early pathology predisposes to lymphatic dysfunction. It should be remembered that during this early stage of LF infection, the subject harboring the adult parasites does not have any evidence of clinical filarial disease and this phase is termed asymptomatic microfilaremia. It has been reported that once established this lymphatic pathology is irreversible even after treatment or death of the filarial parasite and promotes progression of the disease [17].

Once this lymphatic damage progresses, stasis of lymph tends to occur in the dilated vessels due to incompetence of the unidirectional valves in them. This damage is aggravated by bacterial infections of the limb, prolonged standing or strenuous exertion. The transient lympho-paralysis that sets in during acute bacterial infections also abets the lymph stasis. Stagnation of lymph encourages growth of bacteria invading the region. Any interference with the skin integrity of the affected region like injuries, fungal or bacterial infections, fissuring of the skin, and paronychia or eczema favor entry of pathogenic bacteria into the tissues [18,19]. These bacteria, mainly streptococci and occasionally other pathogens, are responsible for the acute attacks of dermato-lymphangio-adenitis (ADLA) commonly seen in filarial limbs [20,21]. Bacteria have been cultured from

the skin and lymph from the edematous limb [22,23].

It is mostly an initial acute attack of ADLA that precipitates lymphedema for the first time in an affected limb, usually starting in childhood. Such repeated attacks later perpetuate and worsen the lymphedema leading to elephantiasis. This in turn favors more such attacks due to lack of local hygiene and a vicious cycle is thus established [4,24]. Advanced stages of lymphedema are characterized by increasing dilation and tortuosity of the lymphatics, endothelial proliferation, formation of new lymph channels, and obstructive changes and dermatosclerosis with nodular and warty changes.

CLINICAL MANIFESTATIONS

The early stage of filarial infection is characterized by presence of live adult parasites in the lymphatic system and mf in the blood, without any outward evidence of disease - the stage of asymptomatic microfilaremia. Once the clinical manifestations develop usually there is absence of microfilaremia and in well-established cases of lymphedema, the circulating filarial antigen indicative of living adult worms is also absent [25]. Lymphedema is a common clinical manifestation of LF that is mostly chronic evolving slowly over the years. Acute attacks of ADLA are also very common and they occur mostly in the limbs or sometimes in the scrotum, in association with lymphedema. Filariasis due to *W. bancrofti* involves the entire affected limb, the genitals, or breasts. Whereas, *B. malayi* infection differs in that the lymphedema involves only the legs below the knee and upper limbs below the elbow, without any genital or breast involvement. But ADLA attacks occur in both infections [26].

Lymphedema and elephantiasis

Lymphedema of extremities is a common chronic manifestation of LF, which on progression results in elephantiasis. Usually the lower limbs are involved, either unilaterally or sometimes bilaterally in which case the swelling tends to be asymmetrical. The upper limbs, male genitalia and rarely breasts in the females may also be affected. The lymphedema of the limbs is commonly graded as follows [27]:

Grade I - Pitting edema, reversible on elevation of the affected limb.

Grade II - Pitting or non-pitting edema, which does not reverse on elevation of the affected limb and there are no skin changes.

Grade III - Non-pitting edema that is not reversible, with thickening of the skin.

Grade IV - Non-pitting edema that is not reversible, with thickening of skin along with nodular or warty excrescences - the stage of elephantiasis.

In advanced stages of lymphedema the skin is thickened and thrown into folds, often with hypertrichosis, black pigmentation, nodules, warty growth, intertrigo in the webs of toes or chronic non-healing ulcers [28]. The swelling may be so huge and grotesque that the patient is incapacitated requiring help even for personal needs. Fungal infections in the interdigital region and in deep folds are a common finding in advanced lymphedema.

Acute dermato-lymphangio-adenitis (ADLA)

The most common acute clinical manifestations in LF are the ADLA attacks. They are usually associated with fever, chills, headache, pain in the involved region, and vomiting. In severe cases there may be toxemia, altered sensorium and urinary incontinence. Though occasionally seen during the early stages of the disease, these episodes are more frequent in higher grades of lymphedema. The affected area, usually in the extremities or sometimes in the scrotum, is extremely painful, warm, red, swollen, and tender. Red streaks may be visible along the inflamed lymphatic vessels. The draining lymph nodes in the groin or axilla may become swollen and tender. The presentation may be with lymphangitis, lymphadenitis, cellulitis, or abscess formation.

In the past, many factors were suggested as causes for these acute attacks. It was assumed that products excreted or secreted by the parasite or exposure to fresh infection with L3 larvae, precipitated ADLA [29,30]. However, it is now recognized beyond doubt that these acute episodes are caused by bacterial infections [18,19,24]. There is also compelling evidence indicating that the filarial worms do not directly cause these [31]. In the affected limbs, lesions favoring entry of such infectious agents can be demonstrated, either in the form of fungal infection in the interdigital spaces, injuries, infections, eczema or fissures in the feet [18,19]. In higher grades of lymphedema, fungal infections occur in the webs of the toes and get aggravated during rainy season or due to household work where the feet are soaked. In such situations the acute attacks are more frequent, abetting the progression of lymphedema to elephantiasis [24]. The fungal infections of the skin act only as entry points for the bacteria and fungi themselves do not cause the ADLA.

Surveys conducted in Pondicherry and Sherthallai in India estimated a frequency of 4.47 ADLA episodes per year for ban-

croftian filariasis and 2.2 episodes for brugian filariasis [32]. On average, such attacks are reported to last for 4 days, but the duration varies with their severity. ADLA tends to be more frequent when the precipitating cause persists as in paronychia, eczema, or severe fungal infection in the webs of toes.

Filarial disease manifestations in children

An important recent development in the epidemiology of LF is the awareness that this infection is first acquired mostly in childhood. Several reports have indicated that children in endemic areas suffer from lymphedema of the limbs, hydrocoele and ADLA attacks [33]. This has also been confirmed by prevalence studies on microfilaremia and filarial antigenemia in children [34,35]. Existence of live adult filarial worms has been shown on Doppler sonography and lymphatic dilatation by lymphoscintigraphy in children aged 3-15 yr [13,15]. This lymphatic pathology in infected children, since it is known to persist, might pave way for future development of disease manifestations. In a study on prevention of ADLA attacks in adult patients with filarial lymphedema, during their interview 32% of the subjects recalled that the disease first manifested before they were 15 yr of age [36].

DIAGNOSIS

In an endemic area, in most patients the clinical diagnosis of filarial lymphedema can be made from the history of evolution of the disease and clinical examination of the affected limb. The usual presentation is with unilateral or sometimes bilateral but asymmetrical swelling of the limbs, which is of long duration and associated with thickening of the skin, along with history of repeated episodes of fever and pain in the affected part indicating ADLA attacks.

The routine tests like night blood examination to detect mf, Immuno-chromatographic-card test (ICT) card test for filarial antigenemia and ultrasonography for locating the adult worms are usually negative once lymphedema is established [25]. Rarely ultrasonography may be used to assess thickening of the tissues in the swollen limbs. Lymphoscintigraphy helps to assess the structural and functional changes in the lymphatics. Lymphatic dilatation, dermal back flow or obstruction to lymph flow in the edematous limbs can be demonstrated by this method.

To assess the size of lymphedema and to observe improvement following intervention, measurements taken at fixed points on the affected limb using a flexible measuring tape or

determination of changes in the volume of the limb by water displacement are useful, especially when repeated at specified intervals.

DIFFERENTIAL DIAGNOSIS

There are diseases other than LF that are known to present with lymphedema and elephantiasis. Practically all the disease manifestations seen in LF can be caused by these conditions as well [37]. Lymphedema from any etiology is prone to ADLA episodes from bacterial infections. Thus primary lymphedema due to congenital anomalies of the lymphatics and secondary lymphedema resulting from malignancy of pelvic structures, irradiation or surgical excision of the lymph nodes or damage caused to the lymphatics due to podoconiosis, are also prone to ADLA attacks [38]. When the disease is advanced, these conditions are clinically indistinguishable from LF. Detailed history of evolution of the disease and clinical examination are usually helpful. In atypical situations, investigations like lymphatic imaging are required to confirm the diagnosis.

MANAGEMENT

Role of drugs acting against filarial parasite

Diethylcarbamazine (DEC) is the drug of choice when there is active infection from *W. bancrofti*, *B. malayi*, and *B. timori*. Though DEC is very effective as a microfilaricidal agent, it kills only around 50% of adult worms. Even though the standard dose of DEC recommended in LF over the years was 6 mg/kg daily for 12 days, recent studies have shown that a single dose of 6 mg/kg is as effective as the 12 days course both against the microfilariae and adult worms [16]. Treatment with DEC does not seem to reverse the lymphatic damage once it is established [17,38]. In early stages of lymphedema DEC may be helpful since there may be an active filarial infection and its use might prevent further lymphatic damage through its macrofilaricidal action. The use of this drug in chronic and advanced cases of lymphedema is not substantiated since it is now known that there is neither microfilaremia nor live adult parasites during these stages. Recent studies indicate that DEC has no role either in the treatment or prevention of ADLA attacks occurring in cases of lymphedema, which are caused by bacterial infections [19,24,39].

The other antifilarial drugs, ivermectin and albendazole, even though important in the sustained reduction of blood

microfilaria levels, have no role in the management of lymphedema or acute attacks.

Treatment of ADLA

The most distressing aspect of disability in LF is attacks of ADLA, which prevent the subject from attending his daily activities for several days during each such episode. In most instances they can easily be treated and further episodes prevented. Bed rest, elevation of affected limb and symptomatic treatment with simple drugs like paracetamol are enough in mild cases. Any local precipitating 'entry lesions' like injury and bacterial or fungal infection should be treated with local antibiotic or antifungal ointments. Moderate or severe attacks of ADL require oral or parenteral administration of antibiotics depending on the general condition of the patient, together with analgesic/anti-inflammatory agents. Commonly used antibiotics like penicillin, doxycycline, ampicillin, amoxicillin or cotrimoxazole may be given in adequate doses till the infection subsides. Bacteriological examination of swabs from the entry lesions may help in selecting the proper antibiotic in severe cases.

Prevention of ADLA

Presently there is a simple, effective, cheap, sustainable, and universally accepted method available for prevention of these attacks. Several studies substantiate the role of proper 'local-hygiene' of the affected limbs, carried out regularly, in preventing ADLA [12,25,31]. Foot care aimed at prevention of fungal and bacterial infections has become the mainstay for disability alleviation in GPELF [36,40]. This procedure requires only the common facilities available for washing in any household and hence can be carried out by the patients themselves in their homes. Patients, community health workers, and also providers of 'home care' can be trained in this foot-hygiene programme, so that the message percolates to all levels in the affected communities, ultimately benefiting every LF patient.

This foot-care programme to prevent ADLA attacks consists of the following [19,24]. Washing the affected area, especially the interdigital region and deep skin folds, with soap and water twice a day or at least once before going to bed and wiping dry with a clean cloth, clipping the nails at intervals and keeping them clean, preventing or promptly treating any local injuries or infections using antibiotic ointments, applying antifungal ointment in the webs of the toes, skin folds and sides of the feet to prevent fungal infections, and also regular use of comfortable foot wear.

In advanced lymphedema proper local hygiene may not always be possible due to deep skin folds or warty excrescences. They may get acute attacks in spite of local care. In such patients, long term antibiotic therapy using oral penicillin or parenteral benzathine penicillin is indicated to prevent ADLA and worsening of lymphedema [19]. In endemic communities, regular foot-care should be encouraged from early age, in view of the fact that LF infection may be acquired in childhood. This would help in preventing acute attacks and the later development of lymphedema in children and young adults.

Treatment of lymphedema

In early stages of the disease if the adult worms are sensitive to DEC, treatment with this drug might destroy them and thus logically prevent the later development of lymphedema [38]. Equally important is the prevention of ADLA attacks in these patients since the occurrence of lymphedema and its progression are related to such repeated episodes [4,19,24]. Established lymphedema cannot be completely cured even though varying degrees of relief is possible with treatment. As mentioned already, treatment with DEC does not seem to reverse the existing lymphatic damage [17,38]. The following treatment modalities offer relief and help to prevent further progression of the swelling:

- 1) Using elasto-crepe bandage or tailor made stockings while ambulant
- 2) Keeping the limb elevated at night, after removing the bandage
- 3) Regular exercising of the affected limb
- 4) Regular light massage of the limb especially in early oedema, to stimulate the lymphatics and to promote flow of lymph towards larger patent vessels
- 5) Intermittent pneumatic compression of the affected limb using single or multicell jackets
- 6) Heat therapy using either wet heat or hot ovens
- 7) Surgical procedures: There are various surgical options available to offer relief of lymphedema, like lymph node-venous shunts, omentoplasty and excision with skin grafting [41]. Even after surgery the local care of the limb should be continued for life, so that ADLA attacks and recurrence of the swelling are prevented [42].

Oral and topical benzopyrones and flavonoids are advocated for the treatment of lymphedema. These drugs are supposed to reduce high protein edema by stimulating macrophages to remove the proteins from the tissues when administered for

long periods [43]. Further controlled trials are needed to substantiate this claim.

Prevention of lymphedema

In lymphatic filariasis, the available evidence suggests that once the lymphatic damage is established it cannot be reversed even with treatment [17]. So this disease has to be prevented, especially in childhood. Primary prevention of lymphedema is achieved by preventing a filarial infection in the 'at risk' population and thus avoiding the early subclinical pathology caused by the adult parasite, which later leads to lymphedema. This is possible through the MDA programme initiated by GPELF in the endemic countries to cover the entire population at risk of contracting filarial infection [7,8].

Secondary prevention is possible through treatment of the early infection by antifilarial drugs acting against adult worms, mainly DEC. This should hopefully prevent progression of the basic lymphatic pathology and thus the manifestation of lymphedema. The foot-hygiene measures mentioned above are helpful in preventing the development of swelling in those who have evidence of LF infection. Physical measures proposed for treatment of lymphedema along with foot-care help to prevent future ADLA episodes and worsening of the swelling and deformity.

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