Lymphology Society of India - Genesis

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Lymphology is the science dealing with Lymphatics, lymphocytes, and lymphoid tissue in health and diseased states. To promote this science the International Society of Lymphology (ISL) was formed in 1966 and its first meeting was held at Zurich - Switzerland. Since then the society meets once in two years as International Congress of Lymphology [ICL]. The membership in the International Society of Lymphology is open to those who are interested in Lymphology and at present there are about 400 members from 34 countries.

In the year 1979 I presented my operative technique - Nodovenous Shunt and Excision for Filarial Edema at the 7th ICL held at Florence, Italy and became a member of the Society. Since then I have attended most of the International Congresses.

During the Congress I came to know that Coumarin reduces Lymphedema and wanted to try it on the filarial patients. So I approached Prof. JR. Casley Smith one of the principal presenters of Coumarin in Lymphedema to try the same on filarial edema cases at Thanjavur Medical College Hospital (TMCH) for inpatient trial, where a 10 bed Filarial clinical Research Ward is functioning. He took up the matter with World Health Organization (WHO) for funding the trial and got the sanction for a double blind clinical trial in 200 patients. With the Govt. of India permission the trail was started in 1983. During the trial Dr. C.K. Rao senior Dy. Director, Minister of Health and Family Planning, Govt. of India and WHO/Filarial Steering Committee member came to inspect the trial on behalf of WHO. He informed me that the Chairman of WHO/FIL steering Committee Dr.E.A. Ottesen is interested in filariasis and doing research at Madras and is currently in Madras and that I could meet him. With Dr. V.Kumaraswami's help I met him and after some discussion I confronted him with "I hear you are studying the immunity in filariasis but I am afraid you may not get any answer because the adult filarial worm live in Lymphatic - the house of immunity activities". I think this impressed him and he agreed to visit Thanjavur Medical College Hospital with Dr. Kumaraswami. After visiting a couple of times and seeing the variety of cases and our successful surgery for elephantiasis and hearing about the ISL he wanted to hold the 12th Scientific meeting of WHO/Filariasis at TMCH, Thanjavur inviting the scientists working on filariasis and reputed lymphologists.

I suggested the names of Drs. JR.Casely Smith, M.H. Witte, Michel Foldi and W.L. Olsewski. The meeting was held in November 1985 and was a great success as it brought together for the first time the scientists working in Filariasis with the lymphologists - both groups interested in lymphatic - but never joined hands in the past. Since then in the International Congress of Lymphology a session is allotted for filariasis. This also paved the way for WHO funded collaborative work in TMCH. Dr. W.L.Olszewski initially studied immuno chemistry and then infecting agents for filarial fever. Dr. M.H.Witte studied Lymphoscintigraphy in microfilarimic and portable gamma micro deducting system to know the lymphatic changes in early filarial infection. Unfortunately we couldn't continue this project since the funding the permission from the Govt. of India didn't materialize.

The WHO meeting at Thanjavur provided the necessary contact with the ICMR scientist working on filariasis at Tuberculosis Research Center (TRC) Chennai and Victor Control Research Centre (VCRC) at Pondicherry and Alappey and attended formal and informal meetings with WHO participants. As a result I came in contact with Drs. V. Kumaraswami,

S.P. Pani, S.K. Kar, R.K. Shenoy who were known for their filarial research work.

I was elected as president of the International Society of Lymphology (ISL) for 1991-93. During my presidency Drs. V. Kumaraswami and S.P. Pani were made as honorary members of the Society and Drs. G. Manokaran and R.K. Shenoy as full members. Dr. M.H.Witte the Secretary General of ISL wanted the International Congress of ISL to be held in India so the lymphologists could see the protean manifestations of Filariasis and our surgery for filarial Lymphedema. To organize and conduct a congress of International stature a Lymphology Society of India should be formed. So Drs. S. Jamal V. Kumaraswami, G. Manokaran, S.P. Pani, M. Snehalatha, Ramkumar, met and decided to from a society and drafted the constitution and bylaws and elected office bearers. The first meeting of the Society was held at Apollo Hospital, Chennai and Dr. P.C.Reddy did the inauguration. The Society was registered on 4th October 1995 as **Lymphology Society of India (LSI)** at Thanjavur with 21 founder members. The signatories to the constitution and bylaws of the society and the office bearers were Drs. G. Manokaran [President] S. Jamal. [Secretary General] V. Kumaraswami, [Treasurer] M. Snehalatha, Ramkumar, S. Balasubramaniam, as executive members and R. Santhalakshmi, And K. Purushothaman as members.

Since then annual general body meeting and conference were held every year. First Conference of the 'Lymphology Society of India' (LSI) was held at Thanjavur in 1996 and Second conference of LSI at Chennai at 1997. During the second meeting it was decided to invite the International Society of Lymphology to hold it's 17th International Congress of Lymphology at Chennai and the same was conveyed and accepted by ISL at Madrid, Spain.

The third conference of LSI was held at Trichy in May 1998 under the presidentship of Dr. M.Farook and the office bearers of the Congress was elected. Drs. S.Jamal [President] G. Manokaran [Organizing Secretary] and V.Kumaraswami [treasurer]

The fourth conference of LSI conference was held in 1999 along with the 17th International Congress of Lymphology (ICL)

The fifth LSI Congress was held in Varanasi in 2000 and the sixth again at Chennai in 2001. The 17th International Congress of Lymphology (ICL) was held at Hotel Park Sheraton, Chennai and Lymphedema Management workshop at Govt. Royapettah Hospital from Sep 19-25, 1999 successfully. The interest from the surplus fund from the conference was earmarked for Lymphedema Research and day to day activities of the Society.

It is expected that the Indian Journal of Lymphology will provide a forum for exchange of ideas and experience among national and international lymphologists and promote Indian Lymphology among other medical fraternity.

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Elimination of Lymphatic filariasis

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Lymphatic filariasis is caused by thread-like parasitic worms which belong to the species *Wuchereria bancrofti, Brugia malayi* and *B. timori.* Lymphatic filariasis strikes early in life. Recent research shows that, in some areas, 30% of children are infected before the age of four years. Clinical disease appears later in life but sub-clinical damage starts at an early age. Lymphatic filariasis is a major cause of disability, social stigmatization, psychosocial and economic reductions in life opportunities, and is a major burden on health and hospital resources and social systems.

It is estimated that close to 120 million people are affected in at least 80 countries throughout the tropics and sub-tropics. One-third of the people affected with the disease live in India, one third in Africa, and most of the remainder in south Asia, the Pacific and the Americas.

Because of its prevalence in remote rural areas, on the one hand, and in disfavoured peri-urban and urban areas, on the other, lymphatic filariasis is primarily a disease of the poor. As many filariasis patients are physically incapacitated, it is also a disease that prevents patients from leading a normal working life. Globally, the disease is the second leading cause of permanent and long-term disability, with the deforming, mutilating disease of limbs and genitals causing not only malfunction but also serious psycho-social consequences. In addition to the direct economic costs of managing the acute and chronic manifestations of lymphatic filariasis, there are enormous indirect losses that follow from diminished productivity and incapacitation and which constitute a severe drain on local and national economies. A recent study in India estimated that the disease cost the Indian economy over a US$ 1 billion annually

Lymphatic filariasis exerts a heavy social burden since chronic complications are often hidden and are considered shameful. For men, genital damage is a severe disability leading to physical limitations and social stigmatization. For women, shame and taboos are also associated with the disease. When affected by lymphoedema, women may be considered undesirable, and when their lower limbs and genital parts are enlarged, they are severely stigmatized; marriage, in many situations an essential source of security, is often impossible.

The Global Programme for the Elimination of Lymphatic Filariasis (GPELF) was launched in response to a World Health Assembly resolution. The goal of the programme is elimination of lymphatic filariasis as a public health problem, and primary, secondary and tertiary prevention of disabilities associated with lymphatic filariasis. Primary prevention is directed at the at-risk population using interruption of transmission by mass drug administration (MDA) to prevent the occurrence of new disease. Secondary and tertiary prevention are aimed at those who are already affected by the disease, and can be achieved using morbidity management as part of home-based long-term care and changing the attitudes of communities.

Interruption of transmission

The approach to interrupting transmission focuses on community-wide administration of a once-yearly single-dose combination of two drugs to entire at-risk populations, either:

- *diethylcarbamazine (DEC)* (6 mg/kg) plus *albendazole* (400 mg – same dose for all ages), a regimen suitable for use only in countries that are free from co-endemic infection with *Onchocerca volvulus* and/or *Loa loa*

or:

- *ivermectin* (150-200 μg/kg) plus *albendazole* (400 mg), a regimen recommended for use in countries, or parts of countries, where *O. volvulus* infection is co-endemic with

bancroftian filariasis (and thus, where DEC is contra-indicated because of the potentially severe side-reactions it can induce in patients with onchocerciasis or loiasis). Areas co-endemic with loiasis are presently excluded.

Whichever of these annual treatment regimens is used, it will need to be continued for a minimum of 4-6 years, i.e. until the adult worms in the body have reached the end of their reproductive life. In programmes where poor coverage is achieved, and hence where some residual transmission may persist, annual treatments may need to continue for a longer period to ensure interruption of transmission.

An additional means of administration is through *regular use of DEC fortified salt*. This strategy needs to be implemented for one year.

It is important to recognize that interruption of transmission through co-administration of drugs in MDA programmes is a form of primary prevention. Because new infections are prevented, individuals will not develop lymphatic damage due to the parasites.

Disability alleviation

Even when microfilariae suppression in blood and interruption of transmission have been achieved, residual lymphatic damage will persist in previously infected individuals, facilitating invasion of the damaged skin and lymphatics by secondary (external, microbial) pathogens. These microbial infections cause local inflammation that can induce or exacerbate lymphoedema and elephantiasis. These individuals constitute the highly visible tip of the iceberg of filarial infection and disease, and though the incidence of such pathology will decline as transmission control is achieved, already affected individuals will require and deserve some form of care to improve their quality of life. Fortunately, new knowledge has made management of such individuals feasible.

During the last decade, the impact of filarial infection on the lymphatics, and the challenge that bacterial infections pose to the compromised lymphatics, have become better understood.

It is now clear that the following measures can both halt progression of elephantiasis and actually reverse the damage already present in many affected individuals. They include:

- Regular washing and drying of the affected parts with soap and water.
- Care of the skin by treating any wounds and using emollients as appropriate.
- Timely, topical use of antiseptics and antifungal or antibiotic creams, as necessary, to treat entry lesions.
- Protecting the skin by use of appropriate footwear.
- Raising the affected limb at night and when possible during the day.
- Regular low intensity movement of the limb.

Acute attacks of acute dermatolymphangioadenitis (ADLA) greatly influence the progression of the disease, and their prevention and treatment is key to the success of disability prevention programmes. Lymphoedema management, through simple measures of skin care and hygiene, leads to improvement in quality of life and thus helps to lessen the public health impact of the disease.

Although a number of surgical interventions are currently used by vascular and plastic surgeons, they are expensive, have a doubtful prognosis, and can be performed only at specialized centres which are clearly beyond the scope of LF programmes. However, the treatment of choice for hydrocele is surgery which requires neither high level facilities nor expertise. The goal of LF programmes should be to increase the access of patients with hydrocele to quality and safe hydrocele surgery.

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A Life Size Human Like Model for Training in Manual Lymph Drainage (Lymph Massage)

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Summary

Lymphoedema is a chronic condition and is not curable, Manual lymph drainage (Lymph massage) is an effective physical therapy method for treating these patients. This procedure can be used lifelong. Ideally performed by a trained physical therapist, it is expensive at present. A human like model for training in manual lymph drainage (lymph massage) has been fabricated. Seventy patients have been trained on it and have been practising the procedure at home as self-help, bringing down the cost of therapy. Also, training is easier on a model than on a patient.

Key Words: Lymphoedema, manual lymph drainage, lymph massage, physical therapy.

Lymphoedema is not curable. It is a chronic condition and has to be managed lifelong[1]. The treatment includes drugs, physical therapy, surgery, psychosocial rehabilitation and their combinations. Conservative therapy has to be continued lifelong, whether surgery is performed or not. Lymph massage (manual lymph drainage) is an important component of physical therapy[2,3]. The procedure should, ideally, be performed by a trained physical therapist.

In our country filarial lymphoedema is widely prevalent and affects mostly poor people. Getting a physical therapist in small places is difficult and to afford his services, lifelong, is all the more difficult, especially, on the part of poor patients. The solution is to train every patient in lymph massage, (manual lymph drainage), so that he/she can perform it at home.

Fig.1 The life size human like model being used for training a patient.

The training is better done on a human like model, since repeated attempt to learn lymph massage on a patient/volunteer will irritate him.

A life size human like model (Fig. 1) has been fabricated. It contains a rigid frame with multiple mobile joints, covered by soft material to impart the feel of the human body. The learner trains on this model repeatedly till his performance is satisfactory. Even, medical and paramedical personnels can be trained on it.

By now seventy patients have been trained on it and have been practising lymph massage at home.

The manufacture cost of this model is about three thousand rupees.

The advantage of this model is that a person can be trained in the procedure without practising on a patient.

The model can be used in lymphoedema treatment centers to train patients. It is inexpensive and, hence, suitable for our country, where filarial lympoedema is widely prevalent.

A patent application for the device is pending.

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Lymphatic Filariasis in Children

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Summary

There is enough evidence indicating that lymphatic filariasis (LF) is a disease acquired mostly in childhood. Many studies have recorded the presence of lymphoedema of the limbs, hydrocoele and acute attacks in children residing in endemic areas. The mf prevalence rates in children were ~ 30% of adult prevalence for < 10 year olds and ~ 69% for 10-19 years olds. The ICT card test showed filarial antigenaemia in 6% of the two-year old children, which increased to 30% in four-year olds. In boys aged 14-16 years, ultrasonography of scrotal lymphatics revealed the existence of adult filarial worms along with diffuse lymphangiectasia. Once established, this lymphatic dilatation is irreversible and causes progression of the disease. Social problems among affected children include feeling of shame, embarrassment, frequent absence from school and even discontinuation of studies. The global LF elimination programme recommending the mass administrations of albendazole along with diethylcarbamazine or ivermectin also targets the problem of geohelminths in children. To alleviate disability, regular foot-care should be practiced from early age, which helps to prevent acute attacks and development of lymphoedema. In endemic areas, this simple and easy to carry out foot-care programme should be included in the school curriculum. Such measures aimed at elimination of LF and prevention of disability should be sustained for several years so that the next generation is saved from this disease.

Introduction

Lymphatic filariasis (LF), an important parasitic disease primarily involving the lymph nodes and lymph vessels of the body, is estimated to infect globally over 120 million people. Ranked as the second most common cause of physical disability (WHO, 1995), LF is still a major public health problem in India accounting for 40% of the world disease burden (Michael et al., 1996). This disease was identified as one of only six potentially eradicable diseases (Centers for Disease Control and Prevention, 1993) and is now targeted for elimination (Ottesen, 1998). There are several indicators to suggest that LF is a disease acquired in the early years of life even though the clinical manifestations are seen mostly in the adults. More importantly, abnormalities of the lymphatic vessels like lymphangiectasia and renal involvement have been demonstrated even in early stages of the infection, when the affected children have only microfilaria in their blood without any overt clinical disease (Dreyer et al., 1992; Witte et al., 1993). Once established, this lymphatic pathology appears to be irreversible and causes progression of the disease leading on to the disfiguring stage of elephantiasis. In the light of these it is quite relevant to discuss how this disease presently affects the health prospects of children and the benefits they would obtain by the elimination of this chronic, disabling and depressing illness from the community.

LF Infection in Childhood

Why did the incidence of LF in the paediatric population did not attract much attention in the past? The foremost reason among them is the natural history of this disease, the early stage of which is remarkably silent and the progression to latter stages is phenomenally slow. It is well known that the early stage of infection is characterized by asymptomatic microfilaraemia, which may continue so for varying periods. These subjects do not have any clinical manifestation of the disease even though they have microfilaria (mf) in their blood, usually detected by night blood examination. Even during this phase, they

are shown to have dilatation of the lymphatics by ultrasonography and lymphoscintigraphy (Noroes et al., 1996; Freedman et al., 1994). The routine stained, thick blood smear examination was found to be not sensitive enough to detect all microfilaraemics when compared to the recently available ICT card test for the detection of filarial antigen in bancroftian filariasis. This is specially so when the density of mf is low or when the infection is in an early stage where the adult worms have not started producing mf (Weil et al., 1997). For this reason, in the past many of these early infections in children were missed. Again many earlier epidemiological studies did not include children less than 5 years.

Evidence for LF in Childhood

Certain epidemiological studies and case reports in the past and more so in recent times; tests for filarial antigenaemia and ultrasound examination of the lymphatics in children - all indicate that LF may be more importantly a disease of childhood (Witt & Ottesen, 2001). At our research centre, the Filariasis Chemotherapy Unit at T.D. Medical College Hospital, Alappuzha, we had observed that among the asymptomatic, microfilaria positive subjects screened during the past 12 years, ~ 30% are aged ≤ 20 years. In our recent study on prevention of ADL attacks in brugian filariasis, during their interview 32% of the subjects recalled that the disease first manifested before they were 15 years of age (Suma et al., 2002).

Clinical manifestations: Several studies have recorded the presence of lymphoedema of the limbs in children from endemic areas for LF, the incidence being higher in older children. Higher grades of oedema are not common since this depends upon the duration of the illness. Hydrocoele of the scrotal sac is also described in boys of pubertal age or older. Acute attacks of ADL were noted in children with lymphoedema (Pani et al., 1991; Ramaiah et al., 1996). The chronic manifestations are seen less often in children < 10 years. Nonspecific lymph node enlargement is a well-known clinical presentation of LF in childhood. Rarely chyluria and tropical pulmonary eosinophilia are described (Witt & Ottesen, 2001).

Microfilaraemia: Studies in different endemic populations on mf prevalence had shown a constant relationship between childhood and adult infections. The childhood mf prevalence rates were shown to be ~ 30% of adult prevalence for < 10 year olds and ~ 69% for 10-19 years olds (Witt & Ottesen, 2001). The microfilaria counts tended to be lower in young children and were higher in older children. Offspring of microfilaremic mothers had higher risk of microfilaraemia when compared to those born of uninfected mothers (Alexander et al., 1998).

Filarial antigenaemia: Longitudinal studies conducted in children from endemic areas have demonstrated filarial antigenaemia in 6% of the two-year olds and the prevalence increased to 30% in four-year olds (Lammie et al., 1998). Test for the adult worm antigen is definitely a more sensitive method than blood mf counts to detect LF prevalence in children. If only the mf detection method by night blood examination is used for diagnosis, at least one-third of all infections would be missed (Witt & Ottesen, 2001).

Ultrasonography: Like in adult males, older children with asymptomatic bancroftian microfilaraemia harbour the adult worms in the scrotal lymphatics. Ultrasound examination of these lymphatics in eight boys aged 14-16 years had revealed the existence of adult filarial worms, indicated by the ‘Filaria dance sign’ (FDS) along with diffuse dilatation of the lymphatic vessels. The FDS was also present in crural lymphatics and axially lymph node in two girls aged 9 and 7 years respectively (Dreyer et al., 1999).

Histopathology: Lymph node enlargement is a feature of LF in children in endemic areas. Biopsy and histopathological studies of these lymph nodes had demonstrated presence of adult parasites (Figueredo-Silva et al., 1994; Dreyer et al., 2001).

Factors Influencing LF Infection in Children:

Many past studies have reported clustering of young individuals with mf in a given household. This has been attributed to several mechanisms.

1. Environmental factors facilitating exposure to infective mosquito bites (Vanamail et al., 1989; 1992).

2. Intra-uterine sensitisation due to maternal infection. Children born to microfilaraemic mothers had higher prevalence of mf (Lammie et al., 1991).

3. Parental infection (maternal, paternal or both) predisposed to higher prevalence of mf in the offspring (Das et al., 1997).

Exposure to infection within the household appeared to be the most important cause for acquiring LF infection in childhood, more than prenatal sensitisation or genetic factors (Das et al., 1997).

Social and Psychological impact of LF in the Young:

Lymphatic filariasis poses several important problems in childhood. Hydrocoele was present in boys aged 10-15 years. Their social problems included feeling of shame, embarrassment and ridicule especially due to hydrocoele. The presence of hydrocoele and lymphoedema even interfered with their conventional school dress. Frequent absence from school due to the acute attacks and sometimes discontinuation of studies in this population would have socio-economic implications for their future (Ramaiah & Kumar, 2000). This chronic disease might thus interfere with the quality of life of these children as they grow up.

Clinical Diagnosis

A child living in endemic areas has a higher risk of developing LF and there is mounting evidence that this parasitic infection is first acquired by many in their childhood. Early diagnosis assumes great importance because the dilatation of the lymphatics, which is the basic pathology induced by the adult worms, appears to be irreversible even with treatment, once it is established (Freedman et al., 1995). This lymphatic dilatation predisposes to lymph stasis, secondary bacterial infections precipitating ADL attacks, development of lymphoedema and its progression (Shenoy et al., 1999). Detection of this disease in the early stages itself and prompt treatment might help to prevent future chronic disability.

Once the subject presents with swelling of the limbs or with an ADL attack, a clinical diagnosis of LF is possible under certain circumstances. Features which help in the diagnosis include the subject residing in an endemic area; familial clustering of such cases; swelling more often unilateral involving the lower limbs or rarely upper limbs; long duration except during initial stages and asymmetry of the swelling when bilateral. The oedema is pitting in early stages, though non-pitting due to thickening of skin in the later stages. There may be enlargement of regional lymph nodes, which are usually tender during acute attacks.

Investigations

Detection of mf by night blood examination: A stained thick smear or filtration using Nuclepore membrane filter is the commonly used method to detect mf for the early diagnosis of LF. MF are usually seen in the night blood smear in the early asymptomatic stage of this infection.

Test for filarial antigenaemia: ICT card test using daytime blood from finger prick is now available to detect the circulating filarial antigen in bancroftian filariasis (Weil et al., 1997). There is no such test at present to detect filarial antigen for the diagnosis of brugia infection. But recently, a recombinant antigen-based immunochromatographic dipstick test called the 'Brugia rapid' has been developed to detect IgG4 antibody in B malayi infection. The evaluation of this test has shown 97% sensitivity, 99% specificity, 97% positive predictive value and 99% negative predictive value (Rahmah et al., 2001).

Ultrasonography: In boys of pubertal age, who have microfilaraemia due to W. bancrofti in the early asymptomatic stage, ultrasonography with

7.5-10 MHz probe has helped to locate the clusters of living adult filarial worms in the scrotal lymphatics in the endemic areas preclinical screening. In younger children, rarely the adult worms were seen in the inguinal and crural lymphatics (Dreyer et al., 1999). Ultrasonography did not help in locating the adult worms of *B. malayi* in the scrotal lymphatics since there is no genital involvement in this infection (Shenoy et al., 2000).

Lymphoscintigraphy: In children this procedure would be useful in certain circumstances to differentiate LF from other congenital causes of lymphoedema. Lymphoscintigraphy helps to assess the structural and functional changes occurring in the lymphatics. After injecting radiolabeled albumin or dextran in the web space of the toes, the lymphatics of the limbs and abdomen are imaged using a Gamma camera. Lymphatic dilatation, dermal back flow or obstruction can be directly demonstrated in the affected limbs by this method. Lymphoscintigraphy was instrumental in demonstrating abnormalities in the lymph vessels even in the early, clinically silent phase of the disease, where the subject had only microfilaraemia (Freedman et al., 1994).

CT, MRI and **MR angiography** are required sometimes to differentiate filarial lymphoedema in children from other causes like malformations of lymph vessels seen in association with certain congenital diseases (Stanton et al., 2000).

Differential Diagnosis

An important aspect of lymphoedema in childhood is that, primary lymphoedema due to various causes may sometimes be found in endemic areas and confused for LF. Such primary lymphoedema in children may be congenital, which manifests shortly after birth or Lymphoedema praecox, usually appearing around puberty. The underlying pathology could be agenesis, hypoplasia or stenosis of lymph vessels. There may be absence of valves in the lymphatics associated with gross dilatation of lymph vessels. There are familial forms of lymphoedema like Milroy's oedema and Meig syndrome.

Though rare, lymphoedema may be seen in association with congenital or hereditary diseases like Turner's syndrome, Noonan syndrome, Yellow nail syndrome, Intestinal lymphangiectasia, Klippel-Trenaunay syndrome or Hyperstomy syndromes. Diagnostic clinical features of the underlying disease could be made out on detailed examination of these children. Where confirmation of the underlying pathology in the lymphatics is required for further management, tests like ultrasonography, CT, MRI or MR angiography of the affected limbs would be useful.

Rarely, bilateral pedal lymphoedema or filarial or non-filarial origin in children in confused for causes of generalised oedema such as hypoproteinaemia, cardiac failure, renal oedema or hypothyroidism. In such situations the oedema tends to be generalised, soft and pitting, bilaterally symmetrical and usually of shorter duration. Examination of different organ systems may reveal evidence of the underlying disease and these conditions are not generally associated with ADL attacks.

Treatment

Antifilarial agents: Diethylcarbamazine (DEC), ivermectin and albendazole are the antiparasitic drugs presently used for the treatment of LF.

Diethylcarbamazine: This is the drug of choice in both *W.bancrofti* and *B.malayi* infections. DEC remarkably lowers the blood microfilaria levels even after single annual doses of 6 mg/kg and this effect is sustained at the end of one year as well (Andrade et al., 1995). DEC also kills the adult worms in over 50% of patients. Ultrasonographic evaluation had shown that single dose of DEC kills the adult worms when they are sensitive to this drug. If they are insensitive, even repeated doses do not have any effect (Noroes et al., 1997).

Eventhough the earlier recommended dose of this drug was 6 mg/kg daily for 12 days, it is known now that a single dose of DEC 6 mg/kg is as effective as the above standard dose (Andrade et al., 1995). Due to the sustained microfilaricidal action even in single annual

doses, this drug is a good tool to prevent the transmission of lymphatic filariasis. The adverse effects produced by the drug result from the rapid destruction of mf and are seen in those subjects who have microfilaraemia. They are characterised by fever, headache, myalgia, sore throat or cough lasting from 24 to 48 hours, which are usually mild and self-limiting, requiring only symptomatic treatment.

Ivermectin: This drug, in single annual doses of 200 to 400 μgm/kg, keeps the blood microfilaria counts at very low levels even at the end of one year. The adverse effects noticed in microfilaraemic patients are similar to those produced by DEC, but are milder due to the slower clearance of the parasitaemia. Ivermectin has no proved action against the adult parasite (Dreyer et al., 1996). In African countries, ivermectin is the drug of choice for prevention of filariasis because of endemicity of Onchocerca and Loa loa infections, where DEC cannot be used due to possible severe adverse reactions.

Albendazole: This well-known anthelmintic drug was shown to destroy the adult filarial worms when given in doses of 400 mg twice daily for two weeks. In males with bancroftian filariasis, the death of the adult worms induced severe inflammatory reaction in the scrotal sac, the common site where they are lodged (Jayakodi et al., 1993). Albendazole has no direct action on the microfilaria and does not immediately lower the MF counts. But when given in annual single dose of 400 mg in combination with DEC or ivermectin, there is sustained lowering of blood microfilaria levels (Shenoy et al., 2000a). Consequent on this effect and its action against many intestinal parasites, albendazole combined with DEC or ivermectin is recommended in the global filariasis elimination programme (Ottesen et al., 1997). Interventions using albendazole offer the advantages of “beyond filariasis” effects of this drug. In children, apart from the effects on intestinal helminths and the consequent anaemia (WHO, 1996), other perceived benefits are gain in height and weight (Beach et al., 1999) and improved performance at school (Nokes et al., 1992).

Treatment and prevention of acute ADL attacks:

Children and young adults suffering from lymphoedema are also prone to acute attacks of ADL, which prevent the person from attending school or other daily activities. These episodes result in considerable suffering and they worsen the oedema status. So their prompt treatment and prevention are of paramount importance.

Bed rest and symptomatic treatment with simple drugs like paracetamol are enough in mild cases. Any local precipitating factor like injury and bacterial or fungal infection should be treated with local antibiotic or antifungal ointments. Moderate or severe attacks of ADL should be treated with oral or parenteral administration of antibiotics depending on the general condition of the patient. Since they result from secondary bacterial infections, systemic antibiotics like pencillin, ampicillin 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.

Treatment and prevention of lymphoedema in Children

In early stages of the disease where the adult parasite is sensitive to DEC, treatment with this drug may destroy the adult worms and thus logically prevent the later development of lymphoedema. Equally important is the prevention of ADL attacks in these patients with underlying lymphatic dysfunction since the occurrence of lymphoedema and its progression are directly related to these repeated infections.

Once lymphoedema is established there is no cure as such as the following treatment modalities offer relief and may prevent further progression of the swelling:

a. Using elasto-crepe bandage or tailor made stockings while ambulant

b. Keeping the limb elevated at night or while resting, after removing the bandage.

c. Regular exercising of the affected limb.

d. Regular light massage of the limb to stimulate the lymphatics and to promote flow of lymph towards larger patent vessels.

a. Annual single doses of DEC 6 mg/kg

b. Annual single doses of ivermectin 200 or 400 μg/kg

c. Annual single doses of combination of albendazole 400 mg with either ivermectin 200 μg/kg or DEC 6 mg/kg. MDA of this combination is recommended for the global LF elimination programme.

d. DEC medicated salt (0.2%) to replace normal cooking salt.

All these methods are useful in reducing transmission of the disease. There use in the population should be continued for at least 5-6 years, due to the long fecundic life of the adult worm.

Vector control: Conventional insecticide sprays, biocides like Bacillus sphaericus and polystyrene beads reduce the breeding of the mosquitoes and thus help in preventing transmission of this disease. These measures should be combined with annual mass chemotherapy for better results. Care should be taken to prevent breeding sites for Culex mosquitoes by avoiding stagnation of water, by deweeding aquatic vegetation and promoting fish farming to destroy the larvae of Mansonia mosquitoes.

Preventing man-vector contact: This can be achieved by using insect repellent creams or insecticide impregnated bed nets and curtains for personal protection.

Conclusion

It is now recognised that lymphatic filariasis is first acquired mostly during childhood. It is also known that the early pathology of this disease, namely the dilatation of lymph vessels, tends to be permanent even with treatment. This lymphangiectasia and stasis favours secondary bacterial infection promoting ADL attacks and progression of lymphoedema. The information that this disease can be eliminated by the judicious use of presently available measures has led to the launching of global LF elimination programme. There is also increased support now for programmes that target younger age groups. The high prevalence of geohelminths in this group has been one of the reasons responsible for recommending the use of albendazole containing regimens
(DEC + albendazole or Ivermectin + albendazole).

Towards disability alleviation, measures like regular foot-care instituted from early age would be useful in prevention of acute attacks and probably in arresting the development of lymphoedema and elephantiasis. Innovative approaches such as introduction of this foot-care programme in the school curriculum in endemic areas would be a progressive step in this direction. It is equally important that these measures aimed at elimination of LF and prevention of disability are sustained for sufficiently long periods so that the future generation is free from this malady.

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Lymphatic Filariasis - Genital Manifestations

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Summary

Patients with genital filariasis are a group of patients who not only have physical disability but also a big psychological problem with poor self esteem and body image. Our study comprising of fifty six patients of genital filariasis of whom forty were males and twenty six females underwent surgical treatment. All patients underwent bilateral nodovenal shunt. In the males this was followed by scrotal reduction for filarial scrotum and circumcision or excision of penile skin and split skin grafting for ram horn penis. The female patients underwent excision of oedematous labia majora alone or along with labia minora in some cases and primary closure or split skin grafting. Post operatively all patients did well. There was cure in not only their physical malady but also removal of their pshychological block due to improved sexual function and body image.

Lymphatic filariasis involving the limbs is very common in India and affects almost forty million people. But genital filariasis excluding hydrocele is not very common for reasons unknown. During the span of last ten years of our surgical practice, we have come across fifty six cases of genital filariasis both male and female.

Materials and Methods: Fifty six patients of genital filariasis were treated of which forty were males and twenty six were females. The age group of the patients varied, the youngest male being fourteen years and the female sixteen years. The oldest male patients with genital filariasis was sixty five years and the female forty five years. Patients with lymphoedema of the lower limbs were excluded from the study. Five patients were diabetic and one female patient was in renal failure.

Male patients presented with filarial scrotum with or without vesicles and lymphorhoea, and ram horn penis. The youngest male patients who was fourteen years old also had chylothorax. Female patients presented with multiple wart like projections or vesicles in the swollen labia majora or only with swelling of labia majora and minora. Pre operative work up included treatment of fungal infection.

Operative technique: All procedures took place under general anaesthesia. All patients underwent a bilateral nodovenal shunt. After one week the male patients with filarial scrotum underwent scrotal reduction. Patient with ram horn penis underwent circumcision with or without excision of the penile skin and split skin grafting. The fourteen year old boy who had filarial scrotum with chylothorax underwent thoracotomy and cauterisaiton of the leaking lymphatic channels combined with a pleuroperitoneal shunt. He also underwent bilateral inguinal nodovenal shunt for the filarial scrotum. Post operatively all were given scrotal support.

The female patients having genital manifestations of lymphatic filariasis underwent bilateral inguinal nodovenal shunt followed by excision of the labia majora and primary closure or split skin grafting.

General measures: All the patients had a cyclical antifilarial and antibiotic therapy, along with removal of focal sepsis and general cleanliness.

Results

All cases were reviewed. The longest follow up was five years and the shortest was six months. Aesthetic appearance, sexual functions and patient satisfaction were recorded in all patients.

Aesthetic appearance was excellent in female patients for whom excision and primary closure

was done as well as in those male patients in whom scrotal reduction was carried out. For penile edema, it is mostly fair and acceptable. Sexual functions in all the cases were normal. On the whole patients were generally satisfied with the results of the surgery.

Discussion

Most of the time patients with genital filariasis are reluctant to see the doctor, unless they are forced by symptoms like discharge, bad odour or loss of sexual function to seek medical help. These patients have a psychological factor, hence convincing them for a surgical procedure builds up their confidence and morale. And after these various surgical techniques as described in this article, most of them are happy in their day today activities.

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Immunopathology of Human Lymphatic Filariasis: Current Status

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Introduction

Lymphatic Filariasis is a mosquito-borne parasitic disease caused by the nematode parasites *Wuchereria bancrofti* and *Brugia malayi* and *Brugia timori* and are the only multicellular parasites to reside in the lymphatics. They are the major cause of human lymphatic filariasis in over ~ 120 million people globally (WHO, report 1998). *Wuchereria bancrofti* is responsible for 90% of cases and is found throughout the tropics and in some sub-tropical areas worldwide. *Brugia malayi* is confined to Southeast and Eastern Asia. *Brugia timori* is found only in Timor and its adjacent islands. Over the last two decades, there has been a flurry of research in filariasis that has provided us insights into the global prevalence, the mechanisms underlying the immunological responses, pathogenesis, control and prophylaxis.

We have focused on the basic aspects of filarial immunobiology by reviewing recent developments and achievements in lymphatic filariasis and get new insights into the possible role of the endosymbiont Wolbachia in mediating inflammatory responses.

Infection and Treatment

The infection is initiated when the infective L3 stage larvae enter the bloodstream during an infective mosquito bite. Over a period of time, these L3 larvae mature into adult worms in the afferent lymphatics draining the extremities and the genitalia. The fecund gravid female releases the microfilariae into the bloodstream from where they are taken up by the mosquito during its blood meal. The microfilariae undergo a series of moultings to develop into L3 stage larvae and the lifecycle continues. However it not quite clear whether a microfilaremic individual will get into a stage of chronic pathology. A single dose of DEC or lvermectin administered once a year is extremely effective in decreasing microfilaremia. A combination of DEC, lvermectin or Albendazole is much more effective than any single drug and safe.

Parasite Survival Strategies

These worms have evolved an arsenal of anti-inflammatory strategies for its survival and transmission. The microfilariae released by the adult females are exposed to a wide variety of the arms of the immune system. The trafficking of the immune cells between the lymphatics and the periphery, allows cross talk between anatomically distinct immunological compartments, resulting in the classical hyporesponsiveness of peripheral blood mononuclear cells observed in most studies. There is a growing interest in the parasite derived molecules and the presence of the endosymbiont Wolbachia, which will be discussed in the following section. Insights into their interaction with the immune system might hold the key for a better understanding of the diverse immunological and clinical manifestations.

What is known about immunological mechanisms in filariasis

Various laboratories including ours have demonstrated that the individuals who harbor microfilaria exhibit antigen specific hyporesponsiveness to filarial antigens compared to patients with chronic pathology and endemic normals. This assessment made by *in vitro* proliferation of peripheral blood mononuclear cells has been supported by the same patients exhibiting low levels of Th1 cytokine response. B cell responses to filarial antigens are only selectively impaired in microfilaremic individuals (Piessens et al., 1980; Nutman et al., 1987). Nevertheless, the levels of parasite specific IgG1,

IgG2 and IgG3 are low in the asymptomatic microfilaremics, with the dominant isotype of anti-filarial antibody being IgG4. The Chronic pathology group exhibits both Th1 and Th2 response while the endemic normals display only Th1. Patients with chronic pathology exhibit higher levels of IgG1, IgG2 and IgG3 antifilarial antibodies when compared to microfilaremics. The development of pathology and the elimination of circulating parasites in symptomatic filarial patients have been attributed to the higher ratio of IgE to IgG4 when compared to microfilaremics (Kurniawan et al., 1993; King et al., 1993). Down regulatory cytokines have suggested to play an important role in the parasite specific T cell energy. Higher levels of IL-10 production spontaneously as well as parasite antigen induced by mononuclear cells from microfilaremics have been reported (Mahanty et al., 1996). Reversal of this down regulation by exogenous addition of IL-12 in *in vitro* studies (Mahanty et al., 1997) underline the critical role of down regulatory cytokines in hyporesponsiveness seen in these patients. This energy has been suggested to be unstable and may break down leading to expression of strong immune responses (Maizels et al., 1991). If the microfilaremic individuals are treated with DEC then their proliferative responses reach normal levels (Suba et al., 2000).

If one looks at these studies in majority of instances only crude filarial antigen has been used for proliferation studies. The crude antigen however contains a mixture of proteins that either may have an immunostimulatory or exhibit an inhibitory effect. More importantly the antigen preparation may also contain proteins derived from the host tissue from which the worms were obtained and there may be batch-to-batch variation in the responses. This problem can be overcome by the availability of gene cloning technology by which a specific gene from the filarial parasite can be identified, cloned and subsequently the protein from this gene can be expressed, characterized and purified. More

important a large amount of data is available on the genome map of the **B.malayi** where in the sequences of several different genes has been obtained experimentally.

We have previously used one recombinant protein from *W.bancrofti* and found enhanced proliferative response even in the microfilaremics (Regunathan et al., 1997). Subsequently, our lab through the interactions of the Filarial Genome Project sponsored by the WHO has produced a few filarial specific recombinant proteins from both *B.malayi* and *W.bancrofti* (Rao et al., 2000; Gnanasekar et al., 2002). One such protein SXP that is recognized by the MF and not by CP or EN has been extensively used by us for developing immunodiagnostic test and a comparison has been made with a standard test like Og4C3 antigen detection assay (Lalitha et al., 2002; Lalitha et al., 1998). Currently we have used this protein WbSXP and examined the functions of PBMCs and macrophages in filarial patients (Sasisekhar et al 2002). In addition to the Th1 response being downregulated in microfilaremics it is possible that the macrophage and dendritic cell function may also be modulated. Phosphorylcholine containing glycoproteins from the parasite have been shown to induce the maturation of Dendritic cells with the capacity to induce Th2 responses. Once the Dendritic cells are differentiated from their precursor cells, they become resistant to changes by the parasite antigen, thus suggesting an impairment of dendritic cell function [Whelan et al., 2000; Semnani et al., 2001]. Previously we have used crude filarial antigens and adherents cells as a source of macrophage and have found no functional change in microfilaremics as observed by the release of GM CSF and TNF alpha (Raman et al., 1999). It is interesting that in *O.volvulus* infections, the recombinant proteins derived from the parasite and the products from Wolbachia exhibit immunomodulatory effects on monocytes function *in vitro* and also promote inflammatory responses (Brattig et al., 2000; Schonemeyer et al., 2001).

Filarial Specific Tolerance

Over the years, it has been established that a profound state of hyporesponsiveness or immunological tolerance exists to filarial specific antigens in asymptomatic microfilaremics. (Piessens et al., 1980). It is not a state of permanent immunological unresponsiveness but a semi-permanent state in which the host becomes effectively tolerized to the parasite burden.

The contemporary model for Th cell activation requires the generation of 2 signals. Signal 1 is generated by the interaction of the T cells receptor with the MHC-peptide complex, while Signal 2 is due to the interaction of the co-stimulatory molecules on the antigen presenting cells with their ligands on the T cells such as CD40:CD40L (Grewal, 1998) and CD80 CD86:CD28 interactions (Jenkins and Schwartz, 1987). The generation of signal 1 alone leads to the inactivation or anergic state of the Th cell. Once anergized, the T cells are unresponsive to specific antigen even if subsequently presented together with adequate co-stimulatory signal(s). Classic observations link peripheral tolerance to antigen presentation. It is possible that the co-stimulatory molecule interactions may be modulated in filarial patients particularly the microfilaremics and could be a contributing factor for the T cell hyporesponsiveness.

Antigenic variation is considered as one of the effective mechanisms of immune evasion. In filariasis, antigenic variation is unlikely to be a primary immune evasion mechanism, as the individual parasites may survive for an average of 8 years or more. Contrary to antigenic variation, the antigens most exposed to immune recognition show extraordinary conservation. The possibility of antigenic conservation playing a role is not clear, but some really good examples for antigenic conservation induced tolerance support this concept. For example homologues of major surface glycoproteins, gp29 from Brugia and Wuchereria and also from onchocerca species show a remarkable degree of antigenic conservation and thus may be involved in tolerance (Maizels et al., 1985; Morgan et al., 1986; Egwang et al., 1988). A further highly

conserved determinant in many proteins is the phosphorylcholine moiety, which is found in many pathogens including the filarial worms that have been shown to evoke strong humoral responses that are not protective and may directly interact with immune cells to down modulate critical responses and thus may induce tolerance (Gualzata et al., 1986; Lal et al., 1990; Maizels et al., 1987).

The mechanisms underlying the impaired immune responses or parasite specific hyporesponsiveness have been postulated to involve adherent suppressor cells, soluble serum suppressive factors, suppressor T lymphocytes etc. These postulated mechanisms had been put to testing where studies with PBMCs have failed to identify any suppressor cell populations. The possibility for the diminished responses due to the absence of antigen responsive lymphocytes also arises due to the fact that PBMCs from microfilaraemic patients fail to produce parasite specific antibodies in response to parasite antigens or Poke Weed Mitogen. Of late there are new concept and postulates into the mechanism of hyporesponsiveness or anergy. Some of these include the alternatively activated antigen presenting cells, the antigen affinity for the T cell receptor (TCR), the prevailing in-vivo cytokine milieu, enzymes of the antigen presenting cells like Burton's Tyrosine Kinase, Indoleamine 2,3 dioxygenase have been shown to inhibit T cell proliferation.

Wolbachia and filarial infections:

A recent and exciting breakthrough in filarial research has been the discovery that endosymbiotic Wolbachia bacteria play an important role in the biology of filarial nematodes (Taylor and Hoerauf, 1999). *Wolbachia* are maternally transmitted intracellular symbionts belonging to the α-proteobacteria known to infect many arthropods and nematodes (Werren and O'Neill 1997, Bandi et al., 1999). These bacteria are abundant in arthropods, where they promote a variety of reproductive manipulations including feminization of genetic males, parthenogenesis and cytoplasmic incompatibility.

The presence of bacteria-like bodies by ultrastructural investigations in the oogonia, oocytes and embryos of filarial nematode, *Dirofilaria immitis* was first reported in the beginning of the 1970s (Harada et al., 1970, Lee, 1975) and these bacteria have been shown to be closely related to the arthropod endosymbiont Wolbachia (Sironi et al., 1995). Subsequently the bacterial nature of these bodies was fully recognized in 1975 and the presence of similar bacteria was reported for other filarial species, including *Brugia malayi* and *Brugia pahangi* (McLaren *et al.,* 1975; Vincent et al., 1975) and tissue distribution and transovarial transmission of the bacteria of *B.malayi* and *Onchocerca volvulus* were then published (Kozek, 1977; Kozek and Figueroa, 1977). Wolbachia endosymbionts are now known to be widespread among filarial nematodes where they are thought to be obligatory symbionts. Ten species out of the 11 species so far examined have been reported to harbor the infection (Bandi et al. 1998). The only species that has not so far been recorded as harboring the Wolbachia is *Acanthocheilonema viteae.*

The presence of Wolbachia bacteria have been revealed by PCR followed by sequencing of the amplified PCR products (Bandi et al., 1998), and confirmed by using electron microscopy studies. Further, immunohistochemical staining of intracellular bacteria in filarial nematodes have been carried out using antibodies against GroEL and Catalase (Henkle-Duhrsen et al. 1998; Hoerauf et al., 1999), both showing high levels of amino acid conservation throughout the proteobacteria.

Electron microscopy studies have shown that intracellular bacteria are present in the lateral cords of both male and female filarial nematodes. Wolbachia have also been observed in the microfilariae and in the second, third and fourth stage larvae (Kozek, 1977, Taylor et al., 1999). However, there are no reports so far about the presence of wolbachia bacteria in the male reproductive system. The presence of large numbers of endosymbionts throughout all stages of the pathogenic filariae of humans suggest that the host will be exposed to Wolbachia following

death of the parasite or through the release of bacterial products.

Phylogenetic relationships among Wolbachia from filarial nematodes and arthropods through the analysis of ftsZ, wsp and 16srRNA genes have shown that there are four main Wolbachia lineages. A and B from arthropods (Werren et al., 1995); C and D from nematodes (Bandi et al., 1998; Bazzocchi et al., 2000). The analyses have provided conclusive evidence to show that Wolbachia from Dirofilaria sp. and Onchocerca sp. form the C lineage, whereas bacteria from *B.malayi, W.bancrofti* and *Litomosoides sigmodontis* form the D lineage.

The currently available phylogenetic data strongly suggest long term association between filarial nematodes and the host. Further, phylogenetic and experimental studies show that the transmission of Wolbachia is strictly vertical. Consequently, the C and D group Wolbachia strains infecting nematodes appear to be more like classical mutualists, being required for normal reproduction and development of their hosts, presumably through the supply of metabolic products required by the worm. Therefore, it is not unreasonable to hypothesize that the biology of *Wolbachia* and their filarial nematode hosts may be tightly intertwined. However, the precise nature of the interaction between *Wolbachia* and filarial worms has not been elucidated.

The Wolbachia-Filarial relationship

A number of reports have investigated the effect of these endosymbionts on host biology. One of the most important and powerful approaches has been the Antibiotic curing, that was originally proposed for arthropod wolbachia and these work have been extrapolated on filarial worms, to understand the effect of antibiotic treatment on these nematodes. Thus endobacterial targeting is now becoming the choice for treatment of human lymphatic filariasis since their depletion by tetracycline led to degeneration and sterility of adult worms (Hoerauf et al., 1999; Taylor and Hoerauf, 1999). It has been shown that th endosymbiotic bacteria living in the host are required for the homeostasis of their host and thus targeting these bacteria leads to sterility of adult worms (Hoerauf et al., 2000). Hoerauf et al., (2001) have demonstrated that depletion of Wolbachia by Doxycycline significantly enhances ivermectin-induced suppression of microfilariemia. This appears to be a potential basis for blocking transmission using a drug-based approach in onchocerciasis. Further, Saint Andre et al., (2002) have demonstrated that when soluble extracts of filarial nematodes were injected into the corneal stroma, and the corneas were subsequently examined by scanning confocal microscopy, the predominant inflammatory response in the cornea was due to species of endosymbiotic *Wolbachia* bacteria and was dependent on expression of functional Toll-like receptor 4 (TLR4) on host cells.

Wolbachia and pathogenesis?

Lymphoedema, elephantiasis and hydrocoel represent the clinical manifestations of human lymphatic filariasis. The development of clinical symptoms occurs several years after exposure to infection and the events leading to the chronic pathology are not understood clearly. However, there is evidence to show the role of inflammatory responses in the pathogenesis and increased levels of inflammatory cytokines such as IL-1beta, IL-6, IL-8 and TNF-alpha and GM-CSF are observed in the fluid from limb lymphoedema and hydrocoel (Olszewski et al., 1992). How this Wolbachia may contribute to these inflammatory responses leading to chronic pathology is still being investigated. There is convincing evidence to show that lipopolysaccharide (LPS)-like molecules in extracts of *Onchocerca volvulus* activate human monocytes to produce to TNF-alpha, via binding to molecules such as CD14 (Brattig et al., 2000). One possibility is that a large number of Wolbachia may be released during acute inflammatory episodes and exposure to Wolbachia by the host may also occur when there is slow destruction of parasites. Sometimes, re-exposure to infective stage larvae, L3 which fail to achieve complete development due to host responses may also release Wolbachia in the host that may contribute to the inflammatory response

associated with chronic pathology. More recently the influence of Wolbachia inflammatory mediators such as LPS on other cell populations was reviewed and hypothesized that LPS can influence the function of a wide variety of other cells such as endothelial and epithelial cells, fibroblasts, lymphocytes, granulocytes, smooth muscle cells, and adipocytes in addition to monocytes and macrophages which are the principal cells responsible for the activation and regulation of innate inflammatory responses (Taylor et al., 2001).

In individuals with circulating microfilariae, however, DEC treatment has shown that Wolbachia are released into the blood following treatment (Cross et al., 2001). Adverse reactions in these individuals are often accompanied by the release of pro inflammatory cytokines such as IFN-gamma, IL-6, IL-1 beta etc and associated with high microfilarial load. The Wolbachia are present in both the adult and the microfilariae, yet the chemotherapeutic killing of microfilariae is invariably associated with acute systematic responses. However, the death of adult worms result in local inflammation and may contribute to the pathology of elephantiasis. The difference in the systemic versus local inflammatory responses is an important issue to be resolved in the near future. Further, identification and morphological localization of antigens, which are recognized increasingly after filarial chemotherapy or doxycycline-treatment of wolbachia endobacteria, might help to find more evidence for the postulated links between filarial fertility, release of endosymbionts, and human immunoreaction.

In our lab we have identified 8 genes of the Wolbachia endosymbiont from the genome of *W.bancrofti* - HSP-60 (GroEL homologue), DNA mismatch repair protein homologues 1 and 2, the DNA polymerase III subunit, the RNA polymerase subunit, the DNA gyrase, succinyl-CoA synthase β-chain, and serine Hydroxymethyltransferase using conserved primers based on **B. malayi** Wolbachia sequences. PCR analysis for the presence of Wolbachia genes is also attempted in the clinical groups of bancroftian filariasis before and after DEC treatment. Wolbachia protein specific antibody levels are also measured in the different clinical groups for better understanding the role of this endosymbiont in the pathogenesis (Identification and characterization of Wolbachia genes is bancroftian filariasis, Suba et al., manuscript in preparation).

Using a similar approach, we identified the presence of the Wolbachia genes Wm-GRO-1 and DNA gyrase in the genome of the filarial cattle parasite, *Setaria digitata.* Sequence analysis reveals that the Gro gene sequence is similar in *B.malayi, W. bancrofit,* and *S.digitata* (with 97% identity at the DNA level). *Setaria digitata* harboring the Wolbachia, thus, should serve as a model for exploring the role of this endosymbiont in the pathogenesis of filarial infections, and for the identification of new chemotherapeutic targets in this important veterinary parasite (Molecular identification of Wolbachia in the filarial cattle parasite, *Setaria digitata*, Suba et al., manuscript in preparation).

In conclusion a lot of information is available on the mechanisms of antigen specific hyporesponsiveness in patients with active filarial infections. However, the functions of accessory cells have not been investigated to a significant extent. The genomics has provided the access to novel genes from both the parasite and the endosymbiont Wolbachia. It is now possible to use the proteins from these novel genes to address the immunological mechanisms more precisely and particularly the antigens involved in the lymphedema formation in filarial patients can be identified. New pathways for intervention and novel targets for immunity could be exploited.

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Lymphoscintigraphy in Clinical Medicine

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The observation by Sherman and Ter-Pogosian that colloidal Au^{198} administered interstitially into the rabbits, localised in drainage lymph nodes provided the foundation for lymphoscintigraphy. This is a minimally invaive procedure. This procedure involves administration of a radiopharmaceutical with subsequent imaging with a gamma camera or detection with a gamma probe. It is based on the principle that radiocolloid when injected into an appropriate areas, retransported by the lymphatics and are localised in drainage lymph nodes. These images provide functional status of the lymphatic system in physiological and pathological status. This technique has largely replaced the more invasive and technically difficult procedure the contrast lymphangiography and also the usage of blue dye in sentinel lymph node (SLN) detection in carcinomas.

Radio tracers

Earlier studies well done with $_{198}$Au. But with subsequent developments after extensive research 99m Technetium (99m Tc) radiopharmaceutical were made available. To study the lymphatic pathways and mapping them, non colloidal macromolecules are adequate. But for clear delineation of lymphnodes, to distinguish subtle features, better normal and abnormal lymphnodes, a colloidal agent with narrow particle size (< 24 nm), good stability, optimal mobilisation with less retention at the injected site and any absence of biological toxicity or antigenicity should be used[1]. 99 m TC HSA (Human serum albumin) is one of the non colloidal macromolecule which is rapidly absorbed and allows shorter study time with better quantification. Various colloidal radio tracer available are listed in Table (1)[2]

	Agent	Particle size
198 Au	Colloid	5 nm; 9 – 15 nm
99m TC	Rhenium sulfide	10 – 40 nm
99m TC	Sulfur colloid	100 – 1000 nm
99m Tc	Antimony sulfur colloid	2 – 15 nm

Route of administration includes subcutaneous, intradermal and subfascial. For superficial lymphatics of the extremities subcutaneous and intradermal would suffice and subfascial for the deep lymphatic system. For the study of upper and lower extremties radiopharmaceuticals are administered into the web space between the digits. For SNL injection were given into the tumor tissue or very close proximity to the tumor. For visualisation of various groups of lymphnodes the site of the injection were listed in Table (2)[3].

	Injection site	Lymph node groups
(a)	Dorsum of the foot	femoral, inguinal, external iliac, para aortic
(b)	Dorsum of the hand	Epitrochlear, axillary, supraclavicular
(c)	Mammary, periareolar, chest wall subcutaneous	Axillary, supraclavicular, upper para sternal
(d)	subcostal posterior rectus sheath	Diaphragmatic, parasternal, internal mammary, mediastinal

(e)	Vulva	Inguinal, external iliac
(f)	perianal, ischiorectal fossa	internal iliac, presacral, obturator, common Iliac, para aortic
(g)	peri tumoral intracutaneous	superficial lympthatics at risk.

Procedure

Images were recorded with a gamma camera either as a dynamic sweep study or a static one in anterior and posterior view immediately after the administration of the radiopharmaceutical. Then the patient performs a stress activity (walking or massage) for 10 minutes (also called stress lymphoscintigraphy). Images are taken as above and also $2-3$ hrs delayed images, stress lymphoscintigraphy enhances the sensitivity of the procedure for lymph flow. A marked changes in the appearance of tracer or clearance indicates a response to intervention. Imaging van be done around the tumoral area including the probable lymph drainage area or a gamma probe can be used to detect radioactivity intra operatively in the case of sentinel lymph node detection.

Lymphoscintigraphy of Lower Extremity Normal Study

Immediate

ANT POST

Familiarity with lymphatic anatomy is essential in the interpretation of the lymphoscintigram. A normal image shows a sequence of discrete radiocolloid aggregates with varied number, intensity of activity reflecting differences in size. The actual size may not be judged. lymphatic channels can be visualised as a linear streak of activity. Liver and splenic activity are seen as these radiocolloids reach the systemic circulation through the thoracic duet.

Clinical Applications

Application of Lymphoscintigraphy included localisation of lymphnodes (SLN and nodes for RT), investigating the cause of lymphedema and assessment of the results of therapeutic interventions in lymphedema.

Lymphedema

It is a swelling of the soft tissues caused by abnormal quantity of lymph due to varied ethology impairing the lymphatic transport. It can be primary secondary which can further be classified as congenital primary and acquired primary lymphedema as shown in Table 3.[4]

Lymphoscintigraphy of Lower Extremity with Lymphedema

Post Exercise Ant Posterior

Classification of Primary Lymphedema

1. Congenital Primary Lymphedema

Aplasia or hypoplasia of lymphatics

Abnormalities of abdominal or thoracic lymph trunks.

Valvular incompetence

Familial (milroy's disease)

2. Acquired Primary Lymphedema

Intraluminal or intramural lymphangio obstructive edema

Obstruction of lymphnodes by hilar fibroses.

3. Secondary Lymphedema

Parasitic (filariasis)

Post surgical

Post traumatic

Malignant

Lymphedema complicating chronic venous insufficiency.

In lymphedema lymphocintigraphy offers objective evidence to distinguish lymphatic pathology from other causes of edema. Lymphatic dysfunctions on a lymphoscintigram include multiple channels. asymmetric flow patterns. delay or absent visualisation of regional lymph nodes, dilated and tortous channels. diffuse flow, dermal backflow and flow through deep lymphatic system (popliteal group of nodes). Quantitative procedures entrance the diagnostic difficulties of borderline uses. [Even through a careful clinical history and examination is adequate in the diagnoses of lymphoedema.] It is possible to conform the etiology on the basis of functional patterns exhibited in the images. Lymphoscintigraphy can be used as an authentic simple noninvasure screening tool in the diagnosis to help in instituting a suitable form of therapy, to highlight the existence of subclinical lymphedema (as in the case of filariasis) and in the follow up.

Postoperative lymphoscintigraphy can identify patients with high risk of development of extremity lymphedema. Early identification of these patients will allow implementation of preventive measures to reduce lymphoedema and also in patients with malignant disease undergoing reconstructive therapy.

Sentinel lymph node detection

As with time sentinel lymphnode concept had taken hold using dye staining of lymphatic drainage from the tumor site, imaging of lymphatic flow to lymphnodes has heightened. Reports on the validity of reliability of SLN histopathological results for the prescence or absence of tumor spread were available. But with the problems faced with the dyes and also its comparitively low sensitivity lymphoscintography shot into prominence[5]

Neoplasm tend to disseminate widely. Staging workup for the patients are essential to establish the extent of the disease, asses prognosis and to determine optimum mode of therapy. To exclude the presence of lymphnode metastases lymphoscintigraphy plays a major role.

Pathological process may become manifest by tumor embolisation of afferent lymphatics blocking the delivery of radiocolloid with demonstration of hold up or hot nodes proximal to obstruction. Invasion of lymphnodes produces aggregates of indistinct borders and decreased radio colloidal capacity. Extensive involvement may result in mallet appearance with tissue infitration into a blush and development of collateral pathways.[3]

SLN staging can be done for various cancers like ca breast[6] ca penis, melanoma[7] pelvic Ca[8] ovarian Ca with internal mammary, Ileopelvic, cutaneous and peritoneal lymphoscintigraphy[3].

In the case of early breast cancer SLN biopsy is being accepted and also in melanoma. Axillary node dissection has a high morbidity with painful arm edema, limitation of arm mobility and paraesthesia.

Approximately 60% of women with early breast cancer have no tumor found at routine staging axillary dissection and do not need the procedure. SLN biopsy shows micrometers more often then does axillary dissection because of the more careful, through histopathological examination that can be done on the SLNs ratio then the multiple nodes dissected during axillary dissection[9]

Conclusion

Interstial lymphoscintigraphy can be easily performed, well tolerated by all age groups, can be repeated and free from local and system toxicity lymphatic flow and sites or drainage can be readily evaluated. It can play an important role in defining the etiology of extremity swelling and in predicting the success of instituted therapies.

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