Filariasis: Making an Early Diagnosis

Uday Sankar Ghosh, Kolkata

OVERVIEW

Filariasis is a disease group affecting humans, caused by nematode parasites of the order Filariidae, and transmitted by mosquitoes - *Culex quinquefasciatus* is globally the most important vector. The adult worms have different habitat in humans like the lymphatic group (Wuchereria bancrofti, Brugia malayi, Brugia timori); cutaneous group (Loa loa, Onchocerca volvulus, Mansonella streptocerca) and body-cavity group (Mansonella perstans and ozzardi). Parasites of the lymphatic group are clinically most significant in our country.

The bulk infection is due to Wuchereria bancrofti (92-98%) and a small percentage is Brugia. Filarial life cycle consists of five larval stages. The third stage larvae (microfilaria) enter the human skin from a mosquito bite, migrate into bloodstream, and eventually reach lymphatic channels where they finally settle down (predominantly in inguinal, scrotal, and abdominal lymphatics) and begin to grow into adult, sexually mature forms that lead to production of abundant amounts of first stage larvae to be taken up by the mosquito again. This may take 6–12 months for a traveller and 2-3 years for an indigenous individual – this is known as pre-patency; the adult worms can live for 5-18 years. Infection usually occurs at very young age (less than 8 years) and has a spectrum of clinical manifestations, however, most often it is asymptomatic (~70%).

Prevalence of microfilaremia increases with age, as adult worms are gradually acquired over years; it stabilizes over the second to third decade. Infected individuals cannot sustain higher levels of parasitemia once they leave the endemic area because the mosquito vector is inefficient. The manifestation of acute and chronic filariasis usually occurs only after years of repeated and intense exposure to infected vectors in endemic areas - mostly late second to fourth decade of life. Most of the asymptomatic infections can ultimately present as chronic complication for which there is no radical cure or any chemoprophylaxis. Filarial diseases are rarely fatal, but the consequences of infection can cause significant disfigurement, impairment of working capacity, personal misery and social stigmatization. WHO has identified lymphatic filariasis (LF) as the second leading cause of permanent and long-term disability after leprosy.

LF is one of the most debilitating neglected tropical diseases and is one of seven diseases worldwide that the WHO has targeted for eradication. In 2000 WHO established the Global Programme to Eliminate Lymphatic Filariasis. The goal of the program is to eliminate LF as a public health problem by 2020 through consecutive annual rounds of mass drug administration (MDA) until interruption of transmission is achieved, and provide care for those who suffer the devastating clinical consequences.

India is one of the five countries with the highest estimated disease burden worldwide (~38%). LF is endemic in 257 districts in 21 states (and union territories); the at-risk population is 600 million with about 31 million having microfilaria and 23 million suffering from disease conditions. Economic losses per year in India are estimated to be around one billion US dollars (~$842) and around 8% of potential male labor force is lost per day per year. The National Filaria Control Program was launched in India in 1955 and now has a goal of elimination of LF by 2015. To ensure success of these ambitions, diagnostic tools, especially early and rapid acting, will play an important role in mapping of endemic areas, monitoring effectiveness of MDA and surveillance for resurgence.
Manifestations can be protean and classified as: 1) **Acute** - Fever with chills and rigors, lymphedema with pain, lymphadenopathy (cervical, axillary, inguinal and generalised – Acute Filarial Lymphangitis/Acute Dermatolympangioadenitis), chyluria, hematuria, inflammatory granuloma or abscesses, pain in testes, funiculitis, epididymoorchitis. 2) **Chronic** - funiculitis, epididymoorchitis, hydrocele, breast edema, elephantiasis. 3) **Asymptomatic** - Endemic normals- negative for Mf but positive for antigens (pre-patency) and asymptomatic microfilaremia - is characterised by the presence of microfilaria in peripheral blood during night but without any overt clinical manifestations of filariasis with or without antigens – also known as MF carriers (patency).1-3,6,8

Factors affecting pathogenesis of filarial manifestations include the cumulative exposure to bites, quantity of accumulating microfilaria and adult worms in different areas of the body which increases with duration.14-16 So, early diagnosis and treatment are the best options. The patients of acute and chronic manifestations usually come for medical attention, while the very big pool of asymptomatic and occult infections, asthmatic bronchitis, any lymph node or any body part can be affected but commonly genital lymphatics are involved in males. 4) **Asymptomatic** - Endemic normals- negative for Mf but positive for antigens (pre-patency) and asymptomatic microfilaremia - is characterised by the presence of microfilaria in peripheral blood during night but without any overt clinical manifestations of filariasis with or without antigens – also known as MF carriers (patency).1-3,6,8

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**DIAGNOSIS**

Most of the clinicians rely on their clinical acumen in the diagnosis of clinical filariasis (low specificity and sensitivity for acute or asymptomatic active infections).15,16 Laboratory tests can be divided into nonspecific and specific tests. Specific tests include - direct detection of microfilaria on blood smears, serologic tests, DNA PCR and radiology. Nonspecific tests are eosinophilia, high IgE levels and lymphoscintigraphy (that reveal dilated lymph channels or backflow even in the early stage of infection).

The direct methods include visualization of microfilaria (or the adult worm) - is made by microscopic examination of thick film of blood collected between 10:00 PM and 2:00 AM, with or without DEC provocation, stained by Geimsa or hematoxylin-eosin for the presence of microfilaria. Adult worm may be found in fluids drawn from swollen areas or serous collections. X-ray tests can show calcified adult worms in lymphatics; ultrasonography can show the "filarial dance".1,2,7 Lymph node aspirate and chylus fluid may also yield microfilaria or worm. Direct diagnosis, though definitive, is difficult, because of timing inconvenience of blood collection, long pre-patency, low patency (<60%) and inadequate sensitivity. Reliance on microfilaria testing may lead to late as well as under diagnosis; it is necessary to develop diagnostics for early detection of the disease.16-18

Early diagnosis of filarial infections is best possible with seromarkers. With the entry of the microfilaria there is a natural IgM response within a few weeks which slowly changes to an IgG response – initially IgG1 and IgG2 – which changes to IgG4 after some more time.11-13 Antigens appear with development of adult worms from microfilaria. This appearance of antigenemia from both adults and the larvae leads to increased easily detectable levels of IgG4. Antibody detection has served as the basis for diagnostic assays for filariasis for many decades, especially with the native antigens. The best of these assays were sensitive for infection but cannot distinguish current infection from past infection or exposure to other parasite and there was significant degree of cross-reactivity with other helminth infections – leading to poor specificity (~40%).15,17

With the advent of recombinant antigens antibody tests have become refined.16,20,21 Antibody-based diagnostic assays using four recombinant antigens, Bm14, WbSXP, BmSXP and BmR1 have become commercially available.22-26 They are based on the detection of antifilarial IgG4 antibodies. The BmR1 ELISA as well as dipstick (Brugia Rapid immunochromatography based) antibody tests have very high sensitivity for Brugia malayi (~100%), Bm14 ELISA is sensitive for both Wuchereria bancrofti and Brugia malayi (~91%-96%), and WbSXP was predominantly sensitive for Wuchereria bancrofti (91%) and somewhat less for Brugia malayi (40%). BmSXP is another recombinant antigen having high sensitivity for Wuchereria bancrofti (95%).25,26 Both WbSXP and BmSXP(WB Rapid) have high specificity for Wuchereria bancrofti (96-99%). A combined test format using BmR1 and BmSXP has been advocated by some as a more comprehensive test of pan filariasis.26,27,28

‘Seva Filachek’ is a dipstick based ELISA system which has been permitted by government of India (Signal MF) for microfilarial antigen(IC-Ag) as well as filarial antibodies (IgG4) in diagnosis of filarial infection in different clinical groups. The detection of IgG4 antibody titre of 1:300 and above against specific microfilarial antigen was found to be useful. Free as well as immune- complexed antigen could also be detected. Overall the test system has a sensitivity and specificity of around 80% for antibody detection and 88%...
for antigen detection.\textsuperscript{27-30} There was no interference from non-filarial helminths or other immune activation states like positive rheumatoid factor, ANF or high levels of IgE. However the problem of specificity especially in the form of distinguishing past from present infection and rarely other helminths remains.\textsuperscript{30} The rapid format assays, though more convenient can give indeterminate result in upto 30% cases, which is unusual in ELISA.\textsuperscript{7-30} The ‘OnSite’ Filariasis IgG/IgM Rapid Test uses conserved recombinant antigens to simultaneously detect IgG and IgM to the Wuchereria bancrofti and Brugia malayi parasites without the restriction on specimen collection. Recombinant multiple beaded antigens including Bm14 and Bm33 from Brugia malayi has been used to follow therapy response by determining IgG4 levels. Bronchoalveolar lavage fluid of patients with tropical pulmonary eosinophilia contains IgE antibodies that recognize Brugia malayi antigen, Bm 23-25.\textsuperscript{28,30}

Filarial Antigen tests, available commercially, are probably better than antibody tests. They show little 24 hour variation in their positivity can detect active infection (better specificity) and have a significantly wider user experience and evidence base for monitoring therapy.\textsuperscript{31-33} This antigen test is available only for infection caused by Wuchereria bancrofti but not for Brugia. Immunochromatographic test (ICT) is a highly sensitive and specific circulating filarial antigen (CFA) detection assay, both as card test (AD-12.1 antibody) and in ELISA based format (Og4C3 antibody— ‘Tropbio’) are now available for the diagnosis of Wuchereria bancrofti infection.\textsuperscript{32-37} This test is positive in early stages of the disease when the adult worms are alive and becomes negative once they are dead. The Card test is a qualitative test with possibility of indeterminate results but very rapid; the Elisa format is a semi quantitative test that provides definite results.\textsuperscript{36-39} Filarial antigen detection has been found to be more useful in epididymoorchitis and allergic disease. Serological tests are the tests of choice for early markers of infection, but they can be hardly used in individuals as the disease is most often asymptomatic - all age group mass screening is the preferred option.\textsuperscript{41,42} Antibody detection provides an early means to detect filarial parasite infection. Presence of IgM antibody to the parasite antigens suggest current infection, whereas, IgG corresponds to late stage or past infection. Utilization of recombinant proteins eliminates cross-reaction.\textsuperscript{43,44} Furthermore, identification of conserved antigens allows ‘pan-filaria’ test to be applicable. However antibody testing is probably better in children. Antigen positivity indicates active disease and it can be used both in sera and body fluids and also in urine and it is the better test considering its specificity. In nearly all antigens positive cases the antibody will be positive and both will be positive in microfilaria positive cases.\textsuperscript{45} Only antibody positivity without antigen or microfilaria may indicate early infection especially the IgM variety but commercial kits for its detection are hardly available.\textsuperscript{11,12}

**CONCLUSION**

With the knowledge of filarial endemicity, its associated morbidities and the national and international intervention strategies for its elimination, it nearly becomes obligatory for any practising doctor to have some working ideas on this disease. Serological tests are the tests of choice for early markers of infection, but they can be hardly used in individuals as the disease is most often asymptomatic - all age group mass screening is the preferred option.\textsuperscript{41,42} Antibody detection provides an early means to detect filarial parasite infection.

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Filarial Lymphedema: Is it the Worm or is it the Host? Ann NY Acad Sci 2002; 979:131-42.


