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RESEARCH AND TRAINING IN TROPICAL DISEASES

INFORMAL CONSULTATION ON EVALUATION OF MORBIDITY IN LYMPHATIC FILARIASIS

TUBERCULOSIS RESEARCH CENTRE

MADRAS, 10-11 FEBRUARY 1992

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1. PURPOSE OF INFORMAL CONSULTATION

An informal meeting was held at the Tuberculosis Research Centre, Madras on 10-11 February 1992 under the joint sponsorship of the Tuberculosis Research Centre, (I.C.M.R.) and the Filariasis component of the Special Programme for Research and Training in Tropical Diseases, (TDR). The participants included physicians, surgeons, epidemiologists, entomologists, parasitologists, clinical pharmacologists, public health planners and members of the TDR Secretariat.

The objectives of the Informal Consultation were:

1. To review the current methods of evaluating the morbidity in lymphatic filariasis.

2. To evolve guidelines for evaluation of acute and chronic forms of the disease which would be useful in large scale multi centric clinical trials.

3. To make appropriate recommendations for the use of these criteria.

2. INTRODUCTION

Lymphatic filariasis is a major health problem in many parts of Asia-Pacific, Africa and South America. There are over 700 million people at risk of developing the disease the world over. It is estimated that nearly 78 million people are infected (mf positives or with clinical disease). The disease is commonly seen amongst the poorest of the poor and has a very low public health rating in the priorities of most countries where it is prevalent.

Two recent initiatives have sought to diminish the misery caused by this disorder. Firstly, the success of ivermectin, a new anti-parasitic agent, which has revolutionized the treatment of onchocerciasis and has been shown to be effective in rapidly clearing the microfilaremia of lymphatic filariasis. The drug is undergoing extensive testing in multi-centric clinical trials to compare its efficacy with the standard drug diethylcarbamazine (DEC). The results obtained so far indicate that the drug is a likely candidate to replace DEC in large scale control programmes. The trials conducted so far have been on asymptomatic microfilaremics and efficacy was assessed by measuring microfilaria levels. The next set of trials planned, seek to assess the relative efficacy of the two drugs in reducing morbidity.

The second initiative that has been taken is to promote research into the socioeconomic aspects of lymphatic filariasis. This initiative, it is hoped, will help to quantify the social and economic burden to individuals, communities and nations. Such quantification will help to unravel the "hidden losses" to communities and also highlight the need to accord a high priority to lymphatic filariasis in the health programmes of nations. In order to estimate the socioeconomic burden it is planned to carry out studies in several endemic areas using common protocols and methodologies. An important constituent of these planned studies is a cross sectional assessment of morbidity. It is obvious that the determination of morbidity at all the centres should be done using uniform criteria.

Till date, clinicians and other health workers have utilized individual methods of assessing morbidity based on their personal preferences and biases. Since no two health workers used the same methods, the literature of lymphatic filariasis is replete with a multitude of definitions, methods and equipment to quantify lymphatic filariasis. Most of them lack precision and reproducibility while others are cumbersome and clearly cannot be carried out under field conditions. In view of the above there is an urgency to standardize criteria to assess and monitor morbidity.

3. CURRENTLY AVAILABLE METHODS FOR EVALUATION OF MORBIDITY

There are no satisfactory definitions of the acute and chronic forms of the disease. Clinicians and health workers broadly agree that certain clinical manifestations are seen sufficiently frequently to be labelled as various "syndromes" in lymphatic filariasis.

3.1 Acute filarial disease

This has until recently been synonymous with "filarial fever". The etiology of these acute episodes is unclear. The presenting features include fever, headache, nausea and vomiting accompanied by local disease. Local disease usually involves either the limbs, male genitalia or the female breast. Local involvement can be recognized by the presence of pain, tenderness, local warmth, lymphangitis and regional lymphadenitis.

Currently available methods for evaluating these episodes rely heavily on the detection of fever and monitoring its course. In addition the presence of other systemic signs and symptoms has been thought to be very characteristic of these features. The accompanying lymphangitis and lymphadenitis have not been accorded sufficient importance.

The assessment of male genital disease has been complicated by attempts to identify the precise anatomical location of inflammation and classify disease accordingly.

3.2 Chronic filarial disease

Lymphoedema of the limbs is the commonest form of chronic disease. Several classifications have been proposed to grade lymphoedema and there is no universally followed system of classification. Some of them are based on the pathological stage of the disease while others rely on anatomical changes that have occurred. Similarly, a number of methods have been used to measure the size and the volume of the limbs. These include simple measurements of circumference at the point of greatest swelling, measurements at many points over both limbs and finally volume measurements (based either on calculations using measurements or by water displacements).

These methods of evaluation are unsatisfactory for several reasons. The lack of standard reference points makes it difficult to have reproducible results. In gross filarial disease it is not uncommon to see gross distortions of the limb accompanied by peculiar protruberences and pockets not to mention warty lesions which are seen in elephantiasis. These gross anatomic changes render accurate measurements of the limb difficult. Volume measurements yield more valuable information but are difficult to carry out and certainly cannot be used in mass surveys. Lastly, where the disease is bilateral the absence of a "control" limb makes assessment more difficult.

Chronic disease of the male genitalia has been even more difficult to grade because the anatomical organization of the affected part does not lend itself to simple measurements. In addition, social custom does not permit a careful enough examination of the genitalia to record changes over time. The same difficulties also exist in the case of examination of the disease of the female breast and genitalia.

4. SUGGESTED SCHEME OF EVALUATION OF ACUTE AND CHRONIC DISEASE

The working groups decided to develop guidelines that would be uniformly used in all the clinical trials using ivermectin and other drugs as also in the cross sectional morbidity surveys which are to be undertaken in the socioeconomic studies on lymphatic filariasis. It was decided to record acute and chronic disease separately using specially designed forms that would allow the data captured to be directly input into computers.

4.1 Acute disease

An acute attack can involve the limbs, scrotum or female breast.

An acute attack involving the limbs would be diagnosed by the presence of the following signs and symptoms, lasting for at least 3 days:

1. Pain
2. Tenderness
3. Lymphangitis and/or lymphadenitis and/or cellulitis
4. Local warmth

An acute attack involving the scrotum would be diagnosed by the presence of the following signs and symptoms, lasting for at least 3 days:

1. Pain
2. Tenderness
3. Clinical features of "epididymoorchitis"
4. Local warmth

An acute attack involving the breast would be diagnosed by the presence of the following signs and symptoms, lasting for at least 3 days.

1. Pain
2. Tenderness presenting unilaterally
3. Lymphangitis and/or lymphadenitis and/or cellulitis
4. Local warmth

In cases involving limbs, scrotum or breast, fever, lymphedema, systemic features such as headache, malaise and vomiting may be present as well. In cases with cellulitis but no lymphangitis or lymphadenitis, filariasis would be diagnosed based on the exclusion of other possible etiologies.

The primary data capture form has been designed to be filled by the primary health worker and has already been tested and modified in a field situation.

4.2 Chronic disease

The working group decided to adopt the classification recommended at the Thanjavur meeting of SWG Filariasis 1985 (Ref TDR/FIL-SWG(12)/85.3). This classification is a modified version of the one used by lymphologists all over the world to grade non-filarial edema. A comprehensive set of guidelines for measurement of affected limbs was also drawn up and includes details such as reference points for measurement and the attitude of the limb during measurement. It also addresses the issue of bilateral disease and has detailed formulae for assessing the volume based on simple circumference measurements. These are based on the observations of Jamal et al (Ref: Ann. Trop. Med. Parasit., (1989), 83, 287), who have used these definitions successfully to study the efficacy of coumarins in lymphatic filariasis.

The group also finalized the methods of measuring chronic disease of the male external genitalia and the female breast. They are based again on simple measurements and have been previously tested in other studies.

5. CLINICAL EVALUATION PROCEDURES

5.1 IDENTIFICATION DATA

1. Name — Date:
2. Sex — Time:
3. Age — Investigator:
4. Id. No.

5.2 Lymphoedema (Limb)

Limb	RUL	RLL	LUL	LLL
1. Grade (see Annex I)				
2. Duration (Yrs)				
3. Pitting				
4. Skin				
Thickening				
Ulceration				
Nodules/warty growth				
Vesicle				
Lymphorrhea				
5. Measurements (see Annex II) in cm				
Points A				
B				
C				
D				
E				

5.3 Scrotal Swelling (Hydrocele)

1. Side
2. Swelling
3. Duration in Yrs
4. Fluctuation
5. Skin changes

   Thickening

   Ulceration

   Nodules

   Lymphorrhea
6. Measurements (see Annex II):

   A:

   B:

5.4 Chyluria (for definition see Annex I)

1. Duration since 1st attack (yrs)
2. Average spell of attack (days)
3. Duration of present attack
4. Description of present attack

   Time of the day when milky urine is passed:

   Morning / Afternoon / Evening / Night

   Presence of blood Yes No

   Pain during voiding of urine Yes No

5.5 Breast Swelling (for definition see Annex I)

1. Side Rt Lt
2. Duration in years
3. Skin
   Thickening
   Ulceration
   Nodules
   Vesicle
   Lymphorrhea
4. Measurements (see Annex II) in cms
   A:
   B:

5.6 Lymph node

1. Site:
2. Side:
3. Number:
4. Size of largest node:
5. Tenderness:
6. Abscess:
7. Scar:

5.7 Female Genitalia Swelling

1. Site:

2. Side:

3. Duration (yrs)

4. Size (if possible)

5. Other descriptions:

5.8 Acute episodes of ADL

The number of acute episodes 1 year prior to and after therapy should be recorded in all cases.

ANNEX I

1. Grades of Oedema

Grade I: Oedema spontaneously reversible on elevation.

Grade II: Oedema not spontaneously reversible on elevation. Skin not thickened.

Grade III: Oedema not spontaneously reversible on elevation. Skin thickened.

Grade IV: Oedema not spontaneously reversible on elevation. Skin thickened with warty/nodular papillomatous growth.

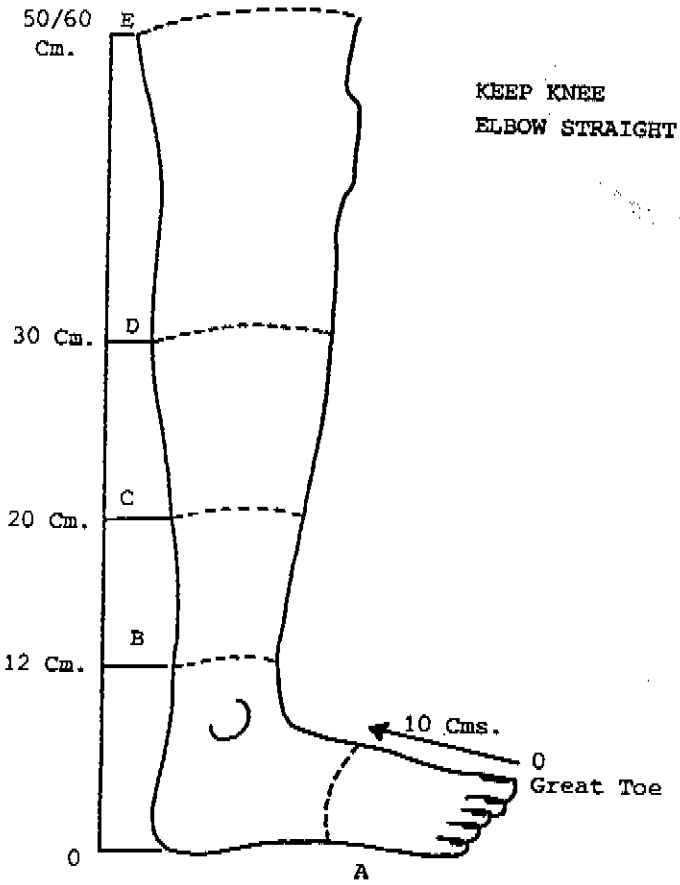
2. Chyluria (Definition)

Passage of uniform milky urine with or without occasional blood stain is chyluria/haemato chyluria. Wherever possible chyluria can be confirmed by qualitative ether solubility test.

ANNEX II

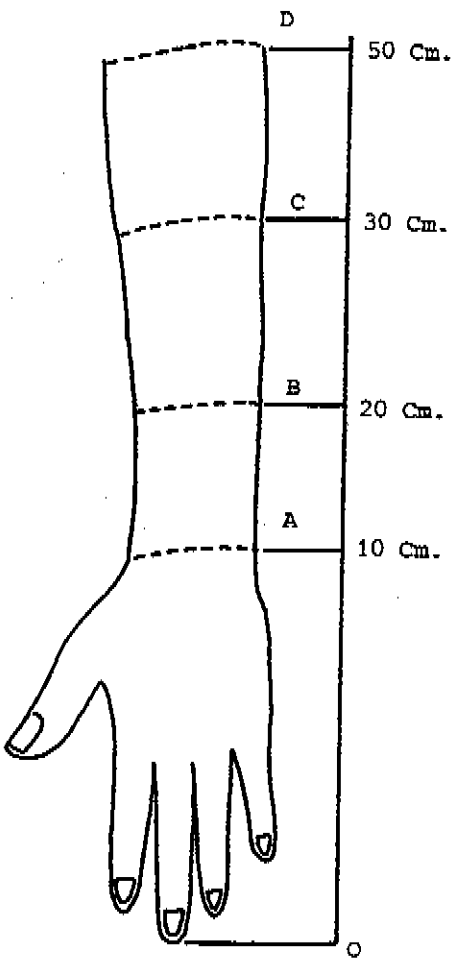
1. Measurement Points for Lymphoedema of Limbs

LL



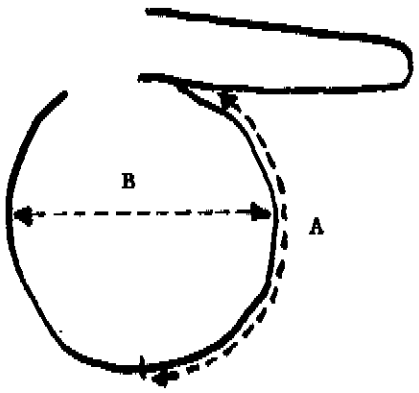
A, B, C, D, E

UL



A, B, C, D

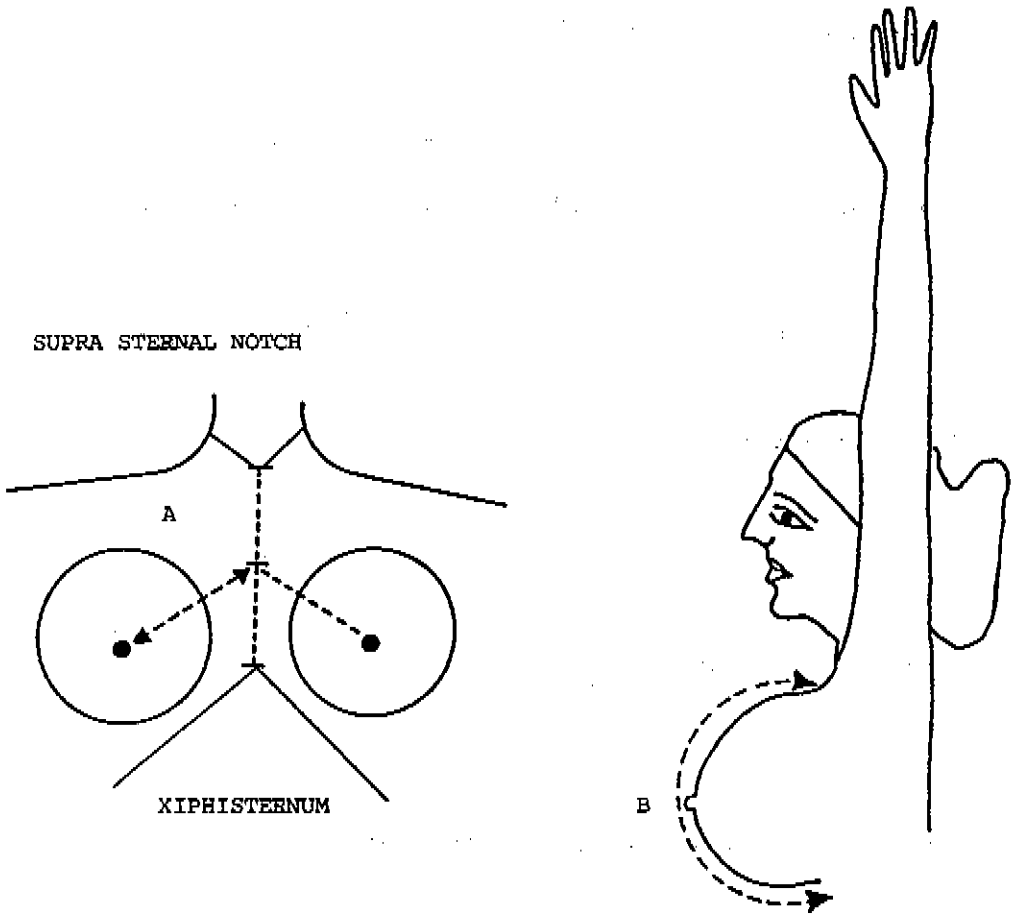
2. Measurement of Scrotal Swelling



A: Between root of penis and lower tip of scrotum anteriorly in the midline of scrotum.

B: The circumference of scrotum at A.

3. Measurement of Breast Swelling



A: Between the midpoint connecting Supra Sternal Notch and Xiphisternum.

B: The circumference from midclavicular point and the lower margin of breast.

ANNEX III

1. Methods of analyses of data for lymphoedema:

Measurements (See Annexure: II):

Time point - 'O'		Time point - 'T'	
Normal limb*	Affected limb	Normal	Affected
A,B,C,D	A_1,B_1,C_1,D_1	A,B,C,D	A_1,B_1,C_1,D_1

Average measurements

X_0 = $\frac{A+B+C+D}{4}$ $\quad$ Y_0 = $\frac{A_1+B_1+C_1+D_1}{4}$ $\quad$ X_T = (as for X_0 and Y_0) $\quad$ Y_T =

DIFFERENCE BETWEEN NORMAL AND AFFECTED LIMB:

$R_0 = Y_0 - X_0$ $\qquad$ $R_T = Y_T - X_T$

R_0 = Initial difference $\qquad$ R_T = Final difference at time 'T'

RESULTS:

Response in individual cases = $\frac{R_0 - R_T \times 100}{R_0}$

Groups (grade of oedema/age/sex etc)

For patients P_1, P_2, P_3, P_4, P_5

Case No.	Initial difference	Final difference
1	P_1R_0	P_1R_T
2	P_2R_0	P_2R_T
3	P_3R_0	P_3R_T
4	P_4R_0	P_4R_T
5	P_5R_0	P_5R_T

AVG R_0 for P_1 to P_5 = Z_0 =

$$\frac{P_1R_0 + P_2R_0 + P_3R_0 + P_4R_0 + P_5R_0}{5 \text{ (Number of patients)}}$$

AVG R_T for P_1 to P_5 = Z_T =

$$\frac{P_1R_T + P_2R_T + P_3R_T + P_4R_T + P_5R_T}{5 \text{ (Number of patients)}}$$

$$\text{Response in the group} = \frac{Z_0 - Z_T}{Z_0} \times 100$$

FOR BILATERAL CASES :

Instead of normal limb one can use average limb measurements for normal healthy individuals - Age, Sex, Ht., Wt., matched .

Age groups:

10-19 yrs

20-29 yrs

30-39 yrs

40-49 yrs

50-59 yrs

60-69 yrs

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