FILARIA ASSOCIATED CLINICAL MANIFESTATIONS IN CHILDREN IN AN ENDEMIC AREA AND MORBIDITY CONTROL BY IMMUNOMONITORING AND OPTIMAL DEC THERAPY: SEVAGRAM EXPERIENCE

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ABSTRACT

Lymphatic filariasis is a major public health problem in India with 412 million people living in bancroftian endemic areas and is a major cause of clinical morbidity. Twenty million people are reported to suffer from chronic disease manifestations such as lymphoedema, hydrocele or elephantiasis. At least twice the number have been shown to suffer from acute and occult filarial infections in an endemic area without diagnosis. Due to non-availability of suitable diagnostic test for confirming filaria aetiology other than parasitological examination, no significant study on filariasis in children has been reported earlier. Studies in our laboratory for more than a decade showed usefulness of microfilarial excretory-secretory antigen in confirming filarial aetiology in acute and occult infections in adults as well as in children. This study reports acute and atypical manifestations such as lymphadenopathy, asthmatic bronchitis, pulmonary eosinophilia, mono-arthritis, recurrent URI, pneumonia, nutritional anemia, pain in abdomen etc. in children living in filaria endemic area having no microfilaraemia but showing filaria aetiology by immunomonitoring for the presence of antibody or antigen and responding to optimal DEC therapy.

KEY WORDS : Filariasis, children, immunomonitoring, morbidity, DEC therapy.

FILARIAL DISEASE AND CLINICAL MORBIDITY

Recent estimates of prevalence of lymphatic filariasis in India revealed that there are about 412 million people living in bancroftian endemic areas in 13 states and 5 UTs. The infection is prevalent in both urban and rural areas. 30 million people are estimated to be harboring *Wuchereria bancrofti* microfilariae and about 20 million suffer with chronic manifestations such as hydrocele (13 million) and lymphoedema (7 million) (1). The clinical manifestations of the disease are crippling physically,

socially and economically. The global burden of lymphatic filariasis was estimated to be at 850, 000 DALYS (Disability Adjusted Life Years) lost and India contributes 38% of the global disease burden. In endemic areas out of 1500 million children in the age group of 0-14 years, 14 million harbour microfilariae, while 1 million suffer with lymphoedema and 2 million with hydrocele (2). In a filaria endemic area patients with acute and occult clinical manifestations far exceed the recorded chronic cases by several times.

IMMUNODIAGNOSIS OF FILARIAL INFECTION

The precise diagnosis of filariasis is presently based on the demonstration of the parasites in the night blood. The parasitological examination of night

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blood is inconvenient, inconsistent and not sensitive in detecting low microfilaraemia. Further, microfilariae are not normally seen in peripheral blood in acute and chronic infections as well as occult filarial infections, making it difficult to confirm active infection in clinical filariasis, for successful treatment. Most of the clinicians rely on their clinical acumen in the diagnosis of clinical filariasis.

In our laboratory, ELISA system has been explored for detecting filarial antibody and antigen using penicillinase enzyme, microfilarial excretory-secretory antigen and antifilarial immunoglobulins (Ig) isolated from clinical filarial sera in diagnosis of filarial infection at different stages. The detection of antibody for specific microfilarial antigen was found to be useful for detecting microfilaraemia and active infection in clinical filarial cases (3, 4). While the filarial IgG antibodies were detected with a sensitivity

of 80% and a specificity of 90% (5), the antigen assay showed a sensitivity of 86% and specificity of 83% in microfilaraemic sera (6). A ten year follow up study on immunomonitoring of 27 microfilaraemic cases during DEC treatment showed that the carriers turn negative for antigen and antibodies with clearance of microfilariae thus confirming that presence of antigen/antibodies may be used as markers of active infection (7, 8). In the absence of microfilaraemia, number of clinical conditions in filarial endemic areas showed presence of either antigen or antibody or both confirming filaria aetiology in our laboratory (4).

Lalitha et. al. (9). reported that the recently introduced monoclonal antibody Og4C3-based ELISA kit in the market (by Tropical Biomedical Institute, Queensland University, Australia) detects circulating filarial antigen only in mf carriers but none

Table 1. Wide spectrum of clinical manifestations in filaria endemic area : Kasturba Hospital based study, 1991-'97

Clinical manifestations	No. screened for Ab	No. positive* for Ab [Ⓐ] (%)	No. screened for Ag	No. positive* for Ag (%)
I. Acute Fever with chills, Lymphadenopathy, Chyluria, Haematuria, Funiculitis & Epididymoorchitis	1867	1298 (70)	644	309 (48)
II. Chronic Lymphoedema, Hydrocele & Elephantiasis	1127	834 (70)	721	316 (44)
III. Occult TPE, Mono & Polyarthrits Tenosynovitis, Glomerulo- nephropathy, Retro-peritoneal lymphangitis, EMF, Iridocyclitis, Recurrent scleritis, Macular oedema, Urticaria & Asthmatic bronchitis.	1389	617 (44)	463	201 (43)
Total	4383	2749 (63)	1828	826 (45)

*Cases showing the presence of filarial antigen/antibody at a serum dilution of 1:300 are considered as positive.

[Ⓐ]Immunomonitoring detected filarial aetiology in acute and occult cases more than twice the number of that of chronic clinical cases.

of the clinical cases. Another monoclonal antibody, AD 12 based ELISA detected circulating filarial antigen in most of the carriers and only in 9 of 64 clinical filarial cases (10, 11).

IMMUNOMONITORING AND MORBIDITY CONTROL IN FILARIAL PATIENTS WITH DEC THERAPY

It has been estimated that about 7.5 million people with lymphoedema and 13 million with hydrocele live in India. Further, millions suffer with acute and occult filarial infections in endemic areas without diagnosis. Treatment of clinical disease groups i.e., acute, chronic and occult filarial cases where mf are always not visible in peripheral blood, has been a challenging problem to the treating clinician. Hence we explored immunomonitoring for the presence of antibody and antigen in suspected clinical cases in the absence of microfilaraemia.

Patient with suggestive clinical history of filariasis and positivity for antibodies or antigen or both is advised DEC (6mg/kg body wt./ day for 21 days in a month) and continued for 3-12 months until the blood sample showed negative reaction for antigen and antibody. The patient is also keen to observe negativity of the test and thus complies with the treatment advice. Complete clinical relief and cure (reversal in cases of minimal hydrocele secondary to epididymo-orchitis and early lymphoedema) without recurrence were observed. Immunomonitoring for presence of antibody and antigen helped in determining optimal DEC therapy (OpDEC therapy) of 3 to 12 months for successful management of individual clinical filarial patient for clinical relief and cure without recurrence (12). Of a total of 4338 suspected filarial cases with clinical manifestations (fever with chills, lymphoedema, lymphadenopathy, epididymo-orchitis, hydrocele, pulmonary eosinophilia, mono and poly arthritis, endomyocardial fibrosis, acute abdomen, asthmatic bronchitis etc.) who attended the Kasturba Hospital, 60% showed positivity for filarial antibodies and 45% for antigen. Filarial antigen detection compared to antibody was found to be more useful in tropical pulmonary eosinophilia and acute epididymo-orchitis (12). Recent analysis of the patients studied in this laboratory (Table 1) showed that the number of acute and occult cases having filarial aetiology was more

than two times the number of chronic clinical filarial cases screened. Of 3,256 suspected acute and occult clinical filarial cases, filarial antibody was detected in as many as 1,915 cases and antigen in 510 cases showing the importance of filarial antibody or antigen detection for confirmation of filaria aetiology in acute and occult filarial infections for successful management.

FILARIAL ANTIBODY AND ANTIGEN IN CHILDREN

Very little is known about filariasis and its associated clinical manifestations in children. It has been reported that in the age group of 0-14 years, in endemic areas 0.96 % of the children were microfilaraemic while 0.07% had lymphoedema and 0.13% had hydrocele (2). Studies on transplacental transfer of filarial infection in microfilaraemic mothers and their offsprings showed that placenta acts as a barrier to transfer of microfilaria and only filarial antigen reaches fetus resulting in filarial antibody positivity in cord blood (13). In our laboratory presence of filarial antibody was detected by stick ELISA using mf ES antigen in 94% of children having classical symptoms and 62% with occult filariasis where as microfilaraemia was observed only in 10% and 1% of these cases respectively (14). Similarly a number of paediatric cases with occult filariasis showing antigen or antibody when treated and followed, responded well to DEC therapy (15). In this hospital in one case of congenital filarial lymphoedema, the neonate of a mother having lymphoedema, had non-pitting, non-tender oedema of right ankle and dorsum of right foot, showed positive reaction for filarial antibody and responded to DEC therapy (16). Another study on filarial antigen, antibody and circulating immune complexed antigen showed that antigen assay was better in microfilaraemic patients where as antibody and immune complexed antigen assays were found to be useful in confirming filaria aetiology in clinical filariasis (4). It was also observed that the prevalence of microfilaraemia among offsprings born to microfilaraemic parents was significantly higher than in those born to amicrofilaraemic parents (17). Lammie et. al. (18) observed an increase in antigen prevalence from 6% among the children of two years old to more than 30% among the children of four years old, but in only one four-year-old child of 156 children,

microfilariae were detected in a 20µl night blood smear. Antifilarial IgG4 response increased significantly among children who acquired infection by four years of age than among children who remained antigen negative. Weil et. al. (19) reported that filarial antigenemia indicative of active filarial infection in healthy normals in an endemic area is more common in above 30 years of age. In another interesting study on clearance of microfilaria and circulating antigen levels monitored by Og4C3 monoclonal antibody assay after 12 weekly doses of 6mg/kg of body weight DEC, marked microfilariae clearance was observed but in no instance did the

antigen level fall to zero, even in individuals that remained microfilariae negative during two or three years follow up (20). Both the antigen assays based on *D. immitis* mab (10) as well as *O. gibsoni* mab (21) were not found to be useful in confirming filarial infection in clinical group and thus no significant studies have been reported on disease group in adults and in particular in children. Amaral et.al. and Noroes et. al. (22, 23) had elegantly studied the characteristic movements of adult filarial worms known as filaria dance sign (FDS) by ultra sonographic study in scrotum and dilated lymphatics in subclinical hydroceles, tropical pulmonary

Table 2. Analysis of blood samples for filarial aetiology in different clinical manifestations in children – a 4 year study

Clinical manifestations	No. examined	No. showing positivity* for filarial		
		Ab (%)	Ag (%)	Ab/Ag (%)
I. Classical filariasis				
1) Lymphoedema	12	6 (50)	8 (67)	10 (83)
2) Lymphadenopathy	19	11 (58)	6 (32)	14 (74)
II. Occult filariasis				
1) TPE	132	66 (50)	63 (48)	101 (77)
2) URI (fever & cough, tonsillitis,pharangitis, myalgia)	118	49 (42)	49 (42)	77 (65)
3) Bronchial Asthma	65	30 (46)	27 (42)	41 (65)
4) Pneumonia	45	16 (36)	16 (36)	24 (53)
5) Nutritional anemia	16	4 (25)	2 (13)	5 (31)
6) Pain in abdomen	9	7 (37)	3 (33)	7 (78)
7) Arthritis	9	4 (44)	5 (56)	8 (42)
8) Others (testicular infections, nephrotic syndrome & anasarca).	16	11 (69)	6 (37)	13 (81)
Total	441	204 (46)	185 (42)	300 (68)

*Cases showing the presence of filarial antigen/antibody at a serum dilution of 1:300 are considered as positive.

eosinophilia (24) and more recently in scrotal and breast areas in children (25). Ultra sound findings often changed after therapy with DEC, with disappearance of dancing worms (26). These studies confirm the presence of filarial adult worms in clinical cases and thus active infection. Thus it is important to have simple and suitable immunoassay for confirming active infection in acute, chronic and occult filariasis and for monitoring during DEC therapy. In our laboratory for more than a decade microfilarial excretory-secretory antigen based antibody (indirect ELISA) and antigen (inhibition ELISA) assays were found to be useful in confirming active filarial infection and determining optimal DEC therapy for clinical relief and cure in adult clinical cases without recurrence (12).

IMMUNOMONITORING IN FILARIA ASSOCIATED CLINICAL MANIFESTATIONS IN CHILDREN

In lymphatic filariasis, as classical clinical cases such as lymphoedema are few in children in endemic areas and as no specific tests were available for occult filarial infection in the past, no attention was given for filaria associated manifestations in children excepting for the tropical eosinophilia. Number of clinical manifestations such as asthmatic bronchitis, upper respiratory tract infection, pneumonia, arthritis, pain in abdomen etc. in children living in endemic area are not screened for filaria aetiology. In Kasturba Hospital associated with our Medical Institute, we introduced the SEVAFILACHEK and explored immunomonitoring for antibody and antigen in clinical cases in the absence of microfilaraemia. Table 2 shows the results of antibody and antigen analysis of 441 children (272 male and 169 female), with ages from 1 to 14 yrs attending Kasturba Hospital with various clinical manifestations that included the cases with classical manifestations (lymphoedema and lymphadenopathy) and occult infections (TPE, bronchial asthma, pneumonia, upper respiratory tract infection, nutritional anemia, arthritis, pain in abdomen and others). Forty six percent of the cases showed presence of antibody and 42% cases showed antigen where as 68% showed the presence of either antigen or antibody. Patients with suggestive clinical history of acute and occult filarial infection and positive for antibody or antigen or both by SEVAFILACHEK are advised DEC (6 mg/kg body

wt./day for 21 days in a month) and monitored quarterly for clinical relief and for the presence of antibody or antigen. DEC treatment is continued until the blood sample showed negative reaction for antigen and antibody. Thus sero conversion (Table 3) helped in determining optimal DEC therapy for successful management of the patient for clinical relief and cure.

This study does show the importance of filaria aetiology in number of atypical clinical manifestations in children in endemic areas for successful management of the patient for clinical relief and cure. Recently ultrasonographic studies (25) have shown the presence of filarial worms in mf positive and mf negative children in filarial endemic areas emphasizing the importance of filariasis in children, the group which was neglected so far. SEVAFILACHEK using mf ES antigen for antibody and antigen assay was found to be very helpful in confirming filaria aetiology and determining optimal DEC therapy along with judicious use of appropriate antibiotics, antihistaminics, analgesics etc. for successful management of children with classical manifestations (lymphoedema, lymphadenopathy) as well as occult infections (TPE, bronchial asthma, pneumonia, upper respiratory tract infection, nutritional anemia, arthritis, pain in abdomen and others).

The management of clinical filarial patients in this hospital by immunomonitoring followed by optimal DEC therapy for clinical relief and cure has attracted attention of the treating physicians in other filaria endemic areas. It has been shown that day time blood collected on filter paper (27, 28) may be used in the immunoassay for filarial antibody and antigen in Stick Penicillinase ELISA (29, 5). Blood samples of filaria suspected patients were collected on filter paper and are routinely received in this laboratory by post from different endemic areas of the country for screening for filariasis as well as for monitoring quarterly for antibody and antigen status for determining optimal DEC therapy. Some of the staff in the endemic areas were provided training on Penicillinase ELISA system and helped in establishing antibody and antigen assay facility for benefit of the patients. Figure shows the centres established for filaria screening test and the places in filaria endemic areas from where blood samples

Table 3. Immunomonitoring and clinical follow up of filarial patients (children) during DEC therapy.

Case No.	Age & Sex	Clinical Manifestation	Duration*of DEC therapy (months)	Filarial Ab positivity		Filarial Ag positivity		Clinical progress
				Before therapy	After therapy	Before therapy	After therapy	
1.	3 F	TPE	3	-	-	+	-	Recovered
2.	6 M	TPE with pain in limbs	3	-	-	+	-	Recovered
3.	8 F	TPE	6	+	-	-	-	Recovered
4.	9 M	TPE	3	+	-	-	-	Recovered
5.	2 M	TPE with joints pain	3	+	-	-	-	Recovered
6.	11 M	TPE	3	+	+	+	-	Recovered
7.	6 M	URI	3	-	-	+	-	Recovered
8.	2 M	URI	3	-	-	+	-	Recovered
9.	3 M	URI with joints pain	3	-	+	+	-	Recovered
10.	9 M	URI	3	+	-	+	-	Recovered
11.	11 M	Lymphoedema	3	+	-	+	-	Recovered
12.	2 M	Lymphoedema	3	+	-	+	-	Recovered
13.	14 M	Lymphoedema	3	+	+	-	+	Mild pain persisted
14.	11 M	Fever	3	+	-	-	-	Recovered
15.	3 M	Arthritis	6	+	+	+	-	Recovered
16.	4 M	LRI	3	+	-	+	+	Mild cough persisted

*DEC was administered 6mg / kg body wt. / day for 21 days each month. TPE-Tropical pulmonary eosinophilia, URI-Upper respiratory tract infection, LRI-lower respiratory tract infection.

Fig. 1. SEVAFILACHEK facilities in India showing the different centres where filaria screening facility is established and different places in filaria endemic areas from where blood samples are received for filaria test.

are received for filaria test. Thus the immunomonitoring has been shown to be very helpful in management of acute and occult clinical manifestations in patients in particular children living in endemic areas.

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