CUMULATIVE EXPOSURE AND ITS RELATIONSHIP WITH CHRONIC FILARIAL DISEASE IN BANCROFTIAN FILARIASIS

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Abstract. Several hypotheses have been put forth about the factors influencing the dynamics of infection and disease in lymphatic filariasis. However, appropriate validation of these hypotheses by real situation analyses of epidemiological data is lacking. The present analyses examine the relationship between cumulative exposure to infection and prevalence of disease by utilizing the existing entomological and clinical data collected between 1981 and 1986 in Pondicherry, South India, endemic for bancroftian filariasis. While there was a significant negative association when the cumulative exposure was correlated with total prevalence of disease ($r = 0.70$, $p = 0.024$) as well as hydrocele alone ($r = 0.74$, $p = 0.014$), a significant positive association was found with prevalence of lymphedema ($r = 0.72$, $p = 0.018$). These results suggest that hydrocele development follows early after exposure, but prolonged exposure could result either in development of lymphedema or immune tolerance resulting in microfilaremia. These could also suggest that the pathomechanisms in development of hydrocele and lymphedema could follow different pathways. Implications of the present findings are discussed in light of the various hypotheses put forward by earlier studies.

INTRODUCTION

In lymphatic filariasis, the process of infection and development of disease is complex. Understanding the dynamics is difficult because of the time lag and the clinical outcome of infections vary widely particularly when chronic pathology is concerned. Most of the epidemiological studies examine the prevalence of infection and disease at a given point of time. These usually show that majority of the microfilaremic people are asymptomatic and most of the symptomatic people are amicrofilaremic (WHO 1984; WHO 1992). In view of these difficulties, the sequence of events involved in disease progression and the factors influencing them are obscure. Several indirect epidemiological and experimental studies have been carried out in this regard and many hypotheses in relation to disease development have been put forth (Beaver,1970; Ottesen, 1984; Partono, 1987; Ottesen, 1989; Srividya *et al,* 1991; Bundy *et al,* 1991; Maizels and Lawrence, 1991; Grenfell *et al,* 1991; Pani *et al,* 1991a; Pani *et al,* 1994b).

Most of the studies carried out so far address two aspects of infection and disease dynamics: sequence of events from infection to disease and factors influencing the development of pathology. Hairston and Jachowski (1968) showed that among the infected people, all who have adult worms irrespective of single sex infections or dual sex infections, develop disease. Later, Srividya *et al* (1991) suggested that probably the individuals go through the following sequence of events: unifected-infected-microfilaremic-amicrofilaremic-diseased. However, further studies have shown that the risk of developing disease in microfilaremic and amicrofilaremic individuals are the same (Pani *et al*, 1991a; Michael *et al*, 1994). Regarding the factors influencing the development of pathology, it has been suggeste that the development of disease could be due to parasite stages (mf, adult, L3, developing worms) or the parasite toxins (Chatterji, 1965) or the immune response of the individual (Beaver, 1970). Subsequently, Ottesen (1984) hypothesized that the type of pathology that an individual develops depends upon the immune status of the individual. Later, Partono (1987) suggested that different clinical manifestations are caused by the different stages of the parasite in the host. Recently again, exposure to L3 larvae has been attributed to the development clinical manifestations (Maizels and Lawerence, 1991; Grenfell *et al,* 1991).

Although the above hypotheses have been put forth, validation of these by epidemiological data is lacking, In one of our recent studies, it was shown

that the microfilaria (mf) prevalence in children less than 10 years of age was a consequence of their cumulative exposure to L3 larvae over the years from the time of their birth (Srividya *et al,* 1994). However, the effect of such an exposure on the development of disease has not been addressed. In this communication, we have adopted an analytical approach to study the relationship between exposure to L3 larvae and its relationship to development of disease. Availability of methods to quantify L3 exposure from entomological data (Vanamail *et al,* 1993), makes it possible to examine the relationship between L3 exposure and development of disease in lymphatic filariasis.

MATERIALS AND METHODS

Data set

A five year Integrated Vector Management programme was implemented from 1981 to 1985 at Pondicherry, South India, endemic for bancroftian filariasis and the details are given elsewhere (Rajagopalan and Das, 1987; Rajagopalan *et al*, 1989; Subramanian *et al*, 1989 Ramaiah *et al*, 1992). Entomological data were collected from 17 catching stations [Larval Evaluating Zones (LEZs)], during the years 1981 to 1985. A door to door clinical survey with specific clinical criteria and physical examination by a team of physicians was carried out in 1986 (Pani *et al,* 1989; Pani *et al*, 1991b). There were 10 LEZs for which both entomological and clinical data were available. Data from these LEZs were used for the present analysis.

METHODS

The Risk of Infection Index (RII) as proposed by Vanamail *et al* (1993), was used to quantify exposure. To examine the possible role of exposure to L3 in the development of disease, disease prevalence in these 10 LEZs was correlated with their corresponding RIIs of the individual years viz, 1981, 1982, 1983, 1984 and 1985 separately. Since it has been suggested that repeated exposure is more important than the exposure during individual years in disease manifestation (Maizels and Lawerence, 1991; Grenfell *et al*, 1991), the RIIs of different years, viz, 81 and 82, 81, 82 and 83, 81, 82, 83 and 84 and finally 81 through 85 were cumulated to quantify the cumulative exposure for 2, 3, 4 and 5 years respectively. Each of these cumulative exposures were then correlated with disease prevalence separately to test for any association between the two. Subsequently life long cumulative exposure was calculated and correlated with disease prevalence.

Calculation of life-long cumulative exposure

Life-long cumulative exposure is more precise when it is calculated using the age of the diseased individuals as it indirectly gives the duration of exposure for development of disease. In this method, we assume that prior to 1981, the transmission was stable and therefore the RII during the years prior to 1981 was the same as that in 1981. For example, when the diseased individual was 15 years of age in 1986, then the sum of RIIs from 82 to 85 will give the exposure he ex-perienced for the last 4 years (*ie* from his 12th year to 15th year) plus the first 11 years of exposure, which was calculated by multiplying the RII of 1981 by 11. Here, the mean age of the diseased individuals was considered and the life long cumulative exposure was calculated using the following equation:

Life-long cumulative exposure for an area =
[(RII in 1981 in that area)* (Mean age of diseased in that area – 4)] + [(Sum of RII from 1982 to 1985 in that area)] ..... (1)

Since mean age is influenced by extreme values, median age was also used in equation (1) and correlated with disease prevalence. However, usage of both mean and median age of the diseased people have limitations in this analyses due to the following reasons: it should be understood that the mean or the median age in the prevalence studies do not suggest the age at which a person develops disease. Since chronic disease in lymphatic filariasis is life long and our interest is to relate exposure to disease development, one should use the age at which different individuals actually developed disease for the first time. In the absence of such details, the minimum age at which a person develops disease in an area was used to calculate the cumulative exposure by the following equation:

Life-long cumulative exposure for an area =
[(RII in 1981 in that area) * (Minimum age of diseased in that area – 4)] + [(Sum of RII from 1982 to 1985 in that area)] ..... (2)

These analyses will indirectly indicate the minimum

Table 1

Relationship between RII and disease prevalence during the different years in different areas.

LEZs	Risk of Infection Index in 1981	1982	1983	1984	1985	Dis prev in 1986 (%)
3	0.098	0.068	0.088	0.048	0.083	6.01
5	0.163	0.090	0.132	0.158	0.119	7.54
14	0.238	0.049	0.046	0.004	0.004	5.47
25	0.047	0.079	0.046	0.002	0.042	6.73
30	0.156	0.040	0.134	0.015	0.048	3.58
32	0.163	0.036	0.033	0.017	0.000	7.47
33	0.026	0.026	0.007	0.000	0.002	8.00
37	0.074	0.062	0.015	0.000	0.004	4.91
39	0.013	0.058	0.000	0.022	0.000	8.74
49	0.082	0.036	0.017	0.011	0.015	7.46
r-value	0.45	0.02	0.49	0.22	0.11	
p-value	0.19	0.95	0.15	0.55	0.77	

duration necessary for development of disease if a person is exposed to a particular level of exposure. This life long cumulative exposure for all the areas was calcutated and tested for its relation with disease prevalence. However, to make the estimates more reliable, the weighted mean of the first three minimum age classes in each area was used. The weights were the number of individuals in that particular age class. The cumulative exposures calculated by replac-ing the minimum age in the equation (2) by the weighted minimum age was then correlated with the overall disease prevalence for different areas.

This analysis was carried not only to see the effect of exposure on the overall disease but also the influence of exposure on the predominant manifestations like hydrocele and lymphedema.

RESULTS

Disease prevalence in 1986 and the RIIs for different years (1981 to 1985) for the different areas are shown in Table 1.

Association of exposure with prevalence of total disease

There was no significant association between the exposure (in terms of RII) during each of the individual years and the prevalence of disease in 1986 (Table 1). Further, there was no significant association when cumulative RIIs of 2, 3, 4 and 5 years were correlated with disease prevalence of 1986 (2 years: ($r = 0.43$, $p = 0.21$); 3 years: ($r = 0.50$, $p = 0.14$); 4 years ($r = 0.32$, $p = 0.37$); 5 years ($r = 0.28$, $p = 0.43$).

Relation between life long cumulative exposure and prevalence of total disease

The cumulative exposure for different areas calculated using the mean age (equation 1) of the diseased individuals also did not show any significant relation with disease prevalence ($r = 0.47$, $p = 0.17$). Similarly, there was no significant correlation between the disease prevalence and the cumulative exposure calculated using median age of the diseased ($r = 0.48$, $p = 0.16$). However, when the minimum age of the diseased individuals in each area was used (equation (2)) for the calculation of

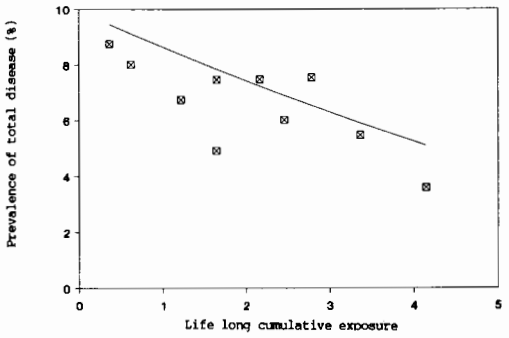

Fig 1–Relation between life long cumulative exposure and prevalence of total disease (Observed; Estimated).

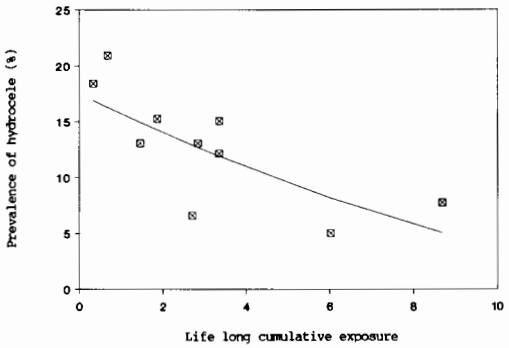

Fig 2–Relation between life long cumulative exposure and prevalence of hydrocele (Observed; Estimated).

cumulative exposure for those areas and correlated with disease prevalence, a significant negative association was found ($r = 0.65$, $p = 0.04$) *ie*, as the cumulative exposure increased, there was a decrease in disease prevalence. When the weighted minimum age was used, the association between the cumulative exposure and overall disease prevalence became even stronger ($r = 0.70$, $p = 0.024$) (Fig 1).

Effect of cumulative exposure on occurrence of hydrocele and lymphedema

Since there is a significant association between the cumulative exposure and prevalence of overall disease, it was desired to see how this exposure influences the development of individual manifestations like hydrocele and lymphedema separately. Using the same weighted minimum age, the cumulative exposure was separately calculated for hydrocele and lymphedema, as the ages of onset for these manifestations are different (Pani *et al,* 1989).

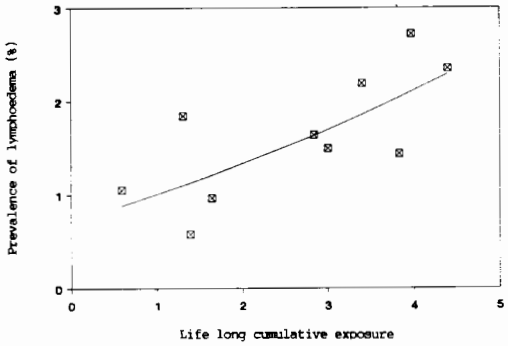

Fig 3–Relation between life long coumulative exposure and prevalence of lymphedema (Observed; Estimated).

The life long cumulative exposure when correlated with prevalence of hydrocele (for males) showed a highly significant negative association ($r = 0.74$, $p = 0.014$). There is a steep decrease in the prevalence of hydrocele as the cumulative exposure increased (Fig 2). But in the case of lymphedema there is a significant positive association ($r = 0.72$, $p = 0.018$), indicating an increase in the prevalence of lymphedema as the cumulative exposure increased (Fig 3).

DISCUSSION

Recent study on the relation between prevalence of mF in children (≤ 10 years) and cumulative exposure indicated that the mF prevalence observed in the children is probably a consequence of their cumulative exposure to the L3 (Srividya *et al,* 1994) *ie,* as the cumulative exposure increases, prevalence of mf also increases. Since microfilaremia is known to result from an immunotolerant status (Maizels and Lawerence, 1991; Lammie *et al,* 1991), this could suggest that repeated exposure could result in immunotolerance. Though it has been hypothesized that exposure to L3 larvae could result in development of disease (Maizels and Lawerence, 1991; Grenfell *et al,* 1991), there has been no validation till date of

these hypotheses using epidemiological data. The present analytical findings have thrown some light on the relationship between the exposure and prevalence of disease in bancroftian filariasis.

Results of these analyses suggest that while the immediate past exposure is not associated with the development of disease, life long cumulative exposure from the time of birth of the individual influences the prevalence of disease. This could suggest that not only the level but also pattern of exposure to L3 influence the clinical consequence. Further, it was found that while the prevalence of total disease and hydrocele were negatively associated with cumulative exposure, prevalence of lymphedema was positively associated with same.

The above findings suggest that the clinical consequence of exposure to L3 is not uniform in a population. It appears that the development of hydrocele could occur (probably in pre-disposed individuals) relatively early after exposure to L3. Since the level of exposure will influence the mating probability of the adult worms in the human host, one would expect that with low level of exposure development of microfilaremia is to be low. Thus it may be possible that unmated worms might be responsible for development of hydrocele. However, individuals who do not develop this manifestation could become immunotolerant due to prolonged exposure and thereby might become microfilaremic. In others, there could be some who due to breakdown of this tolerance after repeated exposure could develop lymphedema (Maizels and Lawerence, 1991; Grenfell *et al*, 1991), probably mediated by an in-effective pro-inflammatory immune response in the individual. Recent studies have shown that the frequency of episodic adenolymphangitis attacks (ADL) per year increase with the progression of lymphedema from one grade to next (Pani *et al*, 1994b). This indirectly suggests the development of these episodic ADL attacks is also related to exposure to L3. Interestingly, it has been seen that the ADL attacks are relatively more common in lymphedema patients than in hydrocele patients. This difference could further support tha the pathogenesis of hydrocele and lymphedema follow two different mechanisms–probably in relation to exposure to L3. Recently, Ottesen (1992) has suggested that development of pathology could be clearly due to two different mechanisms–one due to the presence of immunity and another in the absence of immunity. Although, there is no evidence for the presence of such a mechanismin human host, immunity (whether immune tolerance or breakdown of immune tolerance) could be playing a role in the development of disease which again is apparently related to the level and duration of ex-posure to L3. However, whether the mechanisms we have suggested in light of the present analyses and those suggested by Ottesen (1992) are same or dif-ferent is not known.

In summary, the results of this analyses suggest that the cumulative exposure can cause rapid disease in some (in the form of hydrocele in probably predisposed individuals). In others, repeated exposure could either induce tolerance in some individuals or a pro-inflamatory response is evoked in some, who thereby develop lymphedema (Maizels and Lawerence, 1991). This analyses is the first of its kind which has provided epidemiological background on the relationship between exposure and the development of disease in lymphatic filariasis.

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