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Research Focus

Neonatal tolerance and patent filarial infection

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Lymphatic filariasis occurs in endemic pockets. Patent infections with long-term, high-grade microfilaremia do not develop in nonendemic individuals. It is tempting to speculate that individuals with intact immune responses to filarial antigens are capable of dealing with filarial exposure without developing persistent infection. There are published data that support the idea that only those individuals who are impaired in their immune defense against these parasites owing to neonatal tolerization become productively infected with the filarial parasites. If the model is correct, there are profound implications for global eradication.

Natural history of filarial infection

For most human diseases, our understanding of the natural history of infection is based on the outcome(s) of infection in people who have not experienced the disease previously, that is, naïve populations. Most current models of the course of lymphatic filarial infection, however, have been based on observations on endemic populations. It would, therefore, be instructive to review the literature on the course of filarial infection in previously unexposed individuals to see if such an undertaking would provide any insights into the natural history of the filarial–human interaction.

The filariae are a large group of organisms with diverse habitats in the human host and different outcomes of infection. This review will discuss only the two lymphatic dwelling filariae: *Wuchereria bancrofti* and *Brugia malayi*. The natural course of infection with other filariae (such as *Loa loa* and *Onchocerca volvulus*) is quite different, and will not be discussed here.

There are two different scenarios under which nonendemic persons have been exposed to infection: (i) historical, unplanned events; and (ii) experimental infections. Large numbers of individuals have been moved from nonendemic areas into areas endemic for filariasis as adults. In one example, American GIs (mean age of 26 years) were placed in filaria-endemic South Pacific islands towards the end of World War II. The most comprehensive data come from the Navy. Of 38 300 Naval personnel exposed to filarial infection in the South Pacific Islands [1], a remarkably high number (10 421 individuals or 27.2%) were diagnosed to have contracted acute filarial fever. The diagnosis was based on the classical symptoms of fever associated with lymphadenitis, retrograde lymphangitis and funicitis; retrograde lymphangitis and funicitis are recognized as pathognomonic signs of filarial infection. The timing of the symptoms in relationship to exposure suggests that these individuals had pre-patent infections. These young people were studied extensively, and summarized in 1945 in a US army medical bulletin [2]. Only ~20 of these GIs were ever documented to have developed microfilariae. Even in these rare cases, the microfilaremia was modest and transient.

A second group of nonendemic individuals exposed to filariasis as adults were Indonesians from Irian Jaya who were relocated to Flores [3]. In a review in the CIBA Symposium on Filariasis [3], Partono describes the clinical course of filariasis in previously unexposed migrants. Within two years of migration, a great number of these individuals (18 of 48 individuals or 43%) had evidence of acute filarial infection as manifested by adenolymphangitis. A substantial percentage of them (nine of the 48 or 21%) developed lymphodema or elephantiasis within this period of time. However, only a small percentage (two out of the 48 or 5%) developed microfilaremia. There is, however, a major difference between the American GIs who were exposed to parasites for a limited duration, and the Indonesian transmigrants, who remained in a filariasis-endemic area (see Glossary) for the rest of their lives and were therefore subjected to repeated exposures. The GIs cleared infection without any pathology; the Indonesian transmigrants developed pathology rapidly and at rates that were higher than that seen in endemic populations.

Glossary

Acute disease: There are probably two different mechanisms by which acute symptoms can arise. A small fraction of individuals who live in an endemic area manifest symptoms of acute fever with chills and rigor, lymphadenitis, retrograde lymphangitis and funicitis (inflammation of the spermatic cord). This appears to be a reaction to incoming larvae. In other cases, patients with chronic disease can have acute exacerbations owing to secondary bacterial infection.

Asymptomatic microfilaremics: Individuals who do not complain of any symptoms can be attributed to filarial infection. However, their blood contains circulating microfilariae, often in high numbers. Although they have no overt signs or symptoms, sensitive imaging techniques (such as ultrasound) reveal that they do indeed manifest some pathology that can be attributed to ongoing filarial infection.

Chronic pathology: Patients who have lived in an endemic area for several decades show evidence of sclerotic blockage of lymphatics. Obstruction of lymph flow results in, primarily, the accumulation of intercellular fluid and, secondarily, to the laying down of extracellular matrix. Depending upon the precise lymphatic that is blocked, the manifestation is different. Obstruction of inguinal lymphatics results in swelling of the lower limb, called elephantiasis. Obstruction of spermatic cord lymphatics resulting in the accumulation of fluid in the scrotal sac is called hydrocele.

Endemic area: Geographically defined areas within which the disease (filariasis, in this case) has been reported consistently.

Endemic normals: Individuals who have lived in endemic areas for prolonged periods of time, but do not manifest any signs or symptoms of the disease. If tested, these individuals exhibit humoral and cellular immune reactivity towards filarial antigens, which indicates that they have been exposed.

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Experimental infections of humans

There have been four studies in which L3 larvae were injected experimentally into volunteers [4–7] (for a review, see Ref. [8]). A total of 12 individuals appear to have been injected with substantial numbers of infective larvae. Seven out of 12 individuals in these studies did not become microfilaremic at any time. Only five indivisuals became microfilaremic, all of them transiently. All cleared their infections and remained amicrofilaremic thereafter.

The situation with endemic residents

In an endemic area, in contrast to the nonendemic individuals examined thus far [9], the response to filarial infection has been categorized as 'spectral'. The spectrum

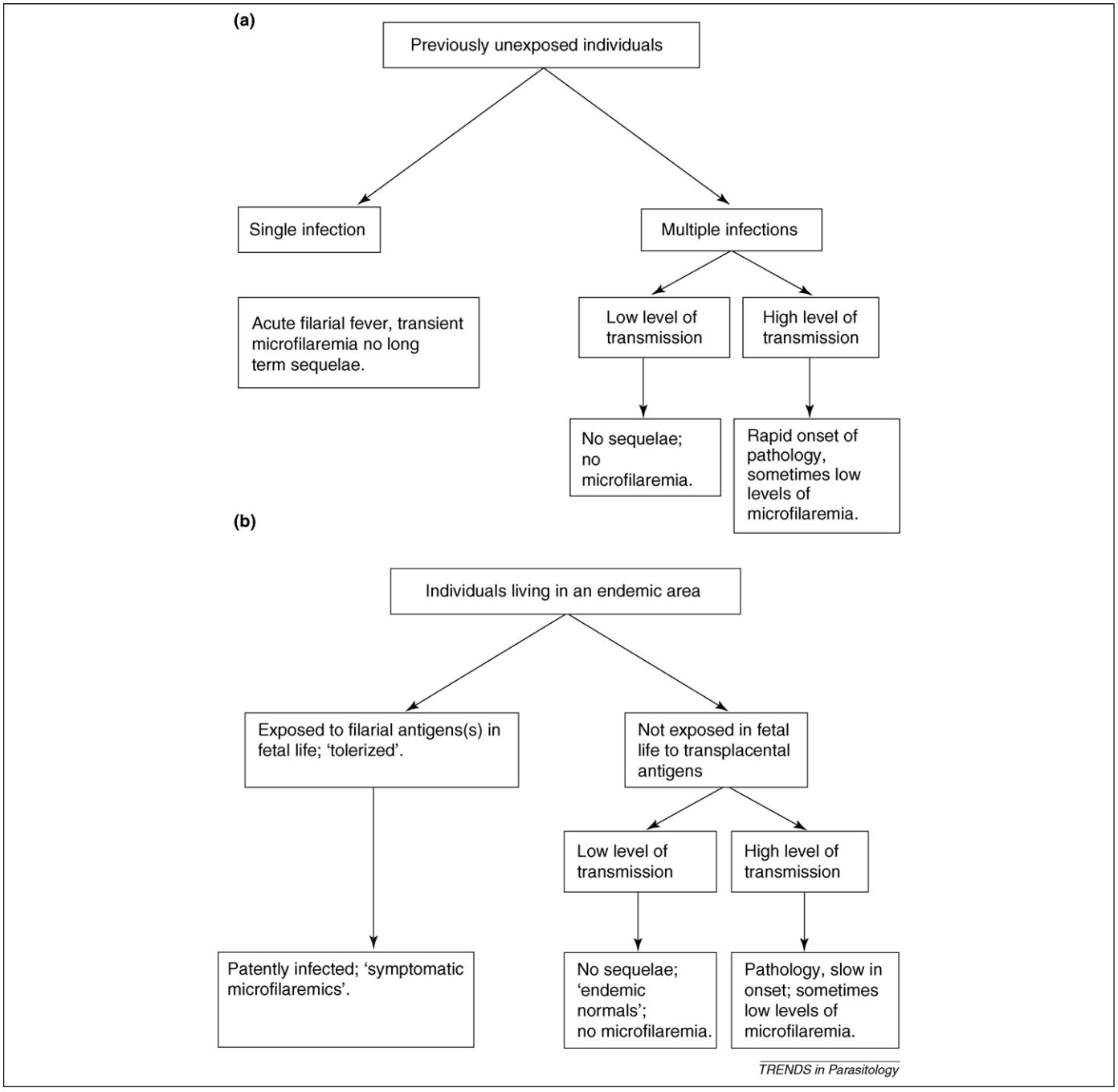

Figure 1. Possible models of the natural history of lymphatic filarial infection. A possible model of the natural history of lymphatic filariasis in **(a)** nonendemic and **(b)** endemic populations, based on data from Coggeshall [1], Beaver [15], Trent [16], Malhotra *et al.* [11], Lammie *et al.* [13] and Steel *et al.* [14]. In the case of nonendemic populations, individuals exposed to infection are immunologically naïve to filarial antigens. The final parasitological outcome of infection is clearance of infection, without the development of persistent microfilaremia. By contrast, the clinical outcome depends on the level of exposure. In the case of single or limited exposure, as in the case of American GIs stationed in the Pacific towards the end of World War II, there is acute disease followed by no further sequelae. In the case of multiple infections, there are no long-term sequelae if the intensity of transmission is low. However, if there is intense transmission, as is the case with the Indonesian transmigrants, there appears to be rapid onset of pathology, with a low incidence of microfilaremia. In the case of endemic populations (b), if individuals have been exposed to infective larval antigens during fetal life, they become tolerized and subsequently permit larvae to mature to adult worms, with the development of persistent microfilaremia (asymptomatic microfilaremics). Individuals who are not exposed to larval antigens during intra-uterine life, are either endemic normals if they are challenged with low levels of infection, or develop chronic disease if they are subjected to heavy parasite burdens.

of responses ranges from the so-called 'endemic normal' who shows no evidence of infection, through to individuals with chronic pathology who might or might not show evidence of microfilaremia. It is tempting to speculate that the endemic normal individuals resemble the US GIs, who experienced a very limited exposure to infection, and who thereafter showed no sign or symptom of filariasis for the 50 years following their exposure to filarial infection in the Pacific. By contrast, individuals with chronic pathology resemble the transmigrants who were exposed to continuous infection.

There is one other phenotype that is observed in an endemic area that has not been described among the nonendemic individuals exposed to filarial infection as adults. These are the so-called asymptomatic microfilaremics, who often harbor large levels of parasites. Microfilaremia levels in the range of several thousand per milliliter of blood are often seen. If most normal, immunocompetent humans possess the immunological machinery to eliminate the infection, why do asymptomatic microfilaremics harbor worms?

In an insightful review, Maizels and Lawrence [10] suggested that immunological tolerance might be the key to lymphatic filariasis. In their view, chronic infection with filarial parasites depresses the immune system and results in maintenance of infection. I would propose that the immunological tolerance precedes, rather than results from, infection and that the tolerization occurs *in utero*. Some recent publications are consistent with this interpretation [11,12]. Lammie *et al.* [13] have examined the effect of maternal parasitemia on the outcome of infection in their offspring. In this cross-sectional study in a village in Haiti, the infection status of mothers, fathers and children was examined. The authors found that, the children of microfilaremic mothers were 2.4- to 2.9-times more likely to be microfilaremic than those of nonmicrofilaremic mothers. By contrast, paternal microfilaremia did not have an impact on the infection status of the children. This important control rules out the trivial explanation that the relationship between maternal infection and that of the children could be simply because of greater exposure within the household. Because the study was cross-sectional, the investigators had no way of ascertaining whether the mothers had been microfilaremic when they became pregnant and remained so during the gestation. However, as microfilaremia is a reasonably stable phenotype, it is likely that these mothers were in fact infected when they were pregnant. Indeed, Steel *et al.* [12] found that 28% of individuals who had been identified as microfilaremic in 1974–1975 in an area of endemic filariasis in the Cook Islands remained microfilaremic in a follow-up study 17 years later.

Steel *et al.* [14] have also examined the impact of maternal infection on the immunological responses of the offspring. Because these authors have been following the endemic population in the Cook Islands over the past two decades, they had longitudinal data of the prior infection status of mothers. They could therefore correlate the immunological status of the children with the microfilaremia status of the mothers at the time of pregnancy. They found that the children of amicrofilaremic (uninfected) mothers exhibited strong cell mediated responses to microfilarial and adult antigens, as judged by T–cell production of interleukin (IL)-2, IL–5, IL–10, and granulocyte macrophage colony-stimulating factor (GMCSF) and interferon gamma (IFN–γ) in response to these antigens. By contrast, children born to microfilaremic mothers exhibited cellular hyporesponsiveness to the same antigens. The hyporesponsiveness was antigen-specific, and did not extend to the nonparasite antigens that they tested. They conclude that these data suggest that the hyporesponsiveness results from *in utero* acquisition of tolerance to microfilarial antigens from chronically infected mothers.

The recent study by Malhotra *et al.* [11] from Kenya is most compelling, because it is a prospective study. These authors recruited 159 newborns from a filariasis-endemic area in Kenya. Eighty-three percent of the cohort were followed for a mean period of 4.3 years after birth. The authors divided the children into three groups. One group was born of mothers who had no evidence of infection. Of the children born of microfilaremic (infected) mothers, they found that cord blood lymphocytes exhibited two patterns. In one group, the cord blood T cells demonstrated filarial antigen-driven IFN–γ, IL-2, IL–5 and IL–13. They termed this group of children 'immune sensitized'. In the remainder, there was no filarial antigen-driven cord blood T-cell responses. They called this group 'immune-tolerant'. They found that there was a 12.9–fold increase in the risk of infection for the immune-tolerant newborns compared with the immune sensitized, and a 4.8–fold increase in the risk of infection compared with the children born of noninfected mothers.

Conclusion

One possible model of the natural course of infection is shown in Figure 1. This formulation of the nature of filarial infections in humans has important implications for the global effort to eradicate the disease. The very fact that humans are inherently resistant to filarial infection implies that once transmission has been lowered to the point that there are not many women in their reproductive phase who are currently infected, filarial infection might not return after one generation. This is an optimistic and encouraging possibility. By contrast, there is a real possibility that individuals who move or are moved from filariasis nonendemic areas to an area where eradication efforts are not underway might develop accelerated disease (similar to the case of the Indonesian transmigrants).

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Prevention of malaria in long-term travelers

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Long-term travellers have a high risk of acquiring malaria, and also of discontinuing malaria prophylaxis. A review by Lin Chen and colleagues addresses the relatively neglected area of malaria prevention in long-term travellers. The essential elements of malaria prevention are discussed: awareness of risk, bite avoidance, chemoprophylaxis, rapid diagnosis, stand-by emergency treatment, and the importance of tailoring recommendations to the individual.

Malaria and global travel

Worldwide travel is increasing, and together with it the risk of acquiring malaria. In the setting of an estimated 300–500 million cases of malaria annually, travellers account for ~30,000 of them (see http://www.who.int/malaria/malariaandtravellers.html). Most current guidelines address prevention of malaria infection in short-term travellers, which reflects the good body of evidence about prevention in this group. However, long-term travellers are an important group, as their risk of acquiring malaria is greater, and their use of preventive measures is often less than that of the short-term traveller. The review by Lin Chen and colleagues [1] is a comprehensive analysis of the literature addressing the relatively neglected area of malaria prevention in long-term travellers, and it provides valuable information and guidance in this area.

The authors defined long-term travellers as those usually residing in areas with no malaria transmission, and travelling for periods of six months or longer in malaria-endemic areas. Other important groups are those who are originally from malaria-endemic areas and who return there to visit their friends and relatives (known as VFR, or visiting friends and relatives, travellers), and temporary migrants who return for good to their home countries [2,3]. The authors divided the elements of prevention into education, personal protection measures, chemoprophylaxis and the use of stand-by emergency treatment and rapid diagnostic tests. This follows an accepted 'ABCD' of malaria prevention: awareness of risk, bite avoidance, compliance with chemoprophylaxis, and the rapid diagnosis of malaria [4] (Box 1).

Awareness of risk

The key elements of any pre-travel consultation are communication and education about travel-associated risks. In the case of malaria this should cover the mosquito-borne route of transmission, the wide range of clinical manifestations in addition to fever, the potential for rapid progression and death, and the need for immediate medical assessment in the event of becoming unwell. Travellers should also know that they could develop malaria many months after their return.

Bite avoidance: personal protection measures

As with short-term travellers, a combined use of different personal protection measures should be recommended; unfortunately, travellers frequently fail to use these consistently. Accepted strategies include minimizing mosquito exposure by spending time indoors between the hours of dusk to dawn, using screens to 'mosquito-proof' living accommodation, trying to eliminate mosquito breeding sites, using insecticides (as mosquito knock-down sprays or to impregnate clothing and bed-nets) and applying repellents to the skin during times of exposure. The key repellents available for use are reviewed: DEET (N,N-diethyl-m-toluamide), picaridin and oil of eucalyptus.

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