Antibodies, prophylaxis, transmission

Opinion

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Elevated levels of immunoglobulin IgE are found in many infections and allergies. IgE is increased in the majority of individuals living in areas of high malaria endemicity. Sotiriades, in 1917, reported clinical improvement in the condition of a patient with acute malaria following the inoculation of 10 ml of serum obtained from a "chronic" case. Kauders confirmed this finding by observing that beneficial effects resulted in 9 of 12 patients who received small quantities of serum from a person difficult to infect with malaria. Plasmodium can give rise to IgE in the absence of other pathogens, such as helminths or other intestinal protozoan parasites, which also are known to induce IgE elevation. IgE in association with monocytes or platelets may trigger reactions that are protective and/or pathogenic. Most children and adults living in areas where the endemicity of *Plasmodium falciparum* malaria is high, have significantly elevated levels of both total IgE antibodies and specific antimalarial IgE bodies in blood. IgE containing immune complexes are known to give rise to monocyte activation via the NO (Nitrous oxide) transduction pathway. A recent study in Nigeria shows that the malaria infection specifically raises IgE, but that IgG and IgM remain virtually stable. There is a strong positive correlation between IgE and parasite density. IgE rises almost exponentially with the severity of the disease [1-9].

An interesting piece of work on this topic comes from Egypt. This study investigated the effect of breast-feeding in protection against protozoan infection in infants with persistent diarrhea. There was a significant positive correlation between the infection intensity and the serum levels of IgE. The levels of IgE and TNF-α were significantly lower in the breast-fed group than in the non-breast-fed group. The percentage of protozoan infections was significantly lower in breast-fed infants [10]. IgE elevations are the expression of $CD4^+$ cells and we have been able to demonstrate that these are increased by the administration of Artemisia annua and Artemisia afra. $CD4^+$ cells are already induced in the pre-erythrocytic stages of malaria. This leads to a wide range of antibodies including some specific against the circumsporozoite protein (CSP) [11,12]. The elevation of specific *Plasmodium falciparum* antibodies is age dependent. The prolonged and repeated exposure to malaria parasites is necessary for the induction of these specific antibodies and there is a significant correlation between their level and the number of malaria attacks [13]. The ability to resist *Plasmodium falciparum* malaria is an important adaptive trait of human populations living in endemic areas. The detection of significant differences in the expression of this trait and the identification of the factors involved should improve the understanding of the host-parasite relationship and might lead to advances in control strategies. In a study in Tanzania it was clearly demonstrated that high anti-*Plasmodium falciparum* IgE levels were associated with reduced acute risk of acute malaria in all age groups, independently of the total IgE level. High levels of IgG either weren't associated with a reduced risk to succumb to a new clinical episode [14].

Reactions to mosquito bites, being immunological in nature, lead to swelling, wheal and flare of the skin. They are due to the mosquito salivary proteins. Mosquito saliva contains many biological materials, anticlotting and antiplatelet factors and vasodilators which presumably increase the speed at which blood from the host is imbibed. But also immunomodulators, allergens which bind to IgE and induce histamine release. Sporozoites express α-gal (galactose-alpha-1,3-galactose), and the bite of mosquitoes like the bite of ticks may lead to an overload with immunoglobulin E antibodies. The molecule α-gal is also present on Trypanosoma and Leishmania parasites [15,16]. Allergens are present in the saliva of most of the mosquitoes, even those which are not infected. A study has shown in a murine model that bites from uninfected mosquitoes prior to Plasmodium yoelii infection influences the local and systemic immune responses and limits parasite development within the host. The difference in liver parasite burdens becomes evident at 20 hours post infection. Another strange way to achieve vaccination! Although the mechanism has yet to be completely elucidated, a similar phenomenon has been noticed: repeated infestation with Ixodes scapularis ticks induces resistance to Borrelia burgdorferi transmission. And multiple exposure to bites from uninfected sand flies prior to infection confer resistance to Leishmania major [17,18]. Repeated exposure to malarial infection could potentially lead to a broadening of antibody specificity. It leads to the boosting of antibodies that are shared by the various parasite strains [19].

In endemic areas specific antibodies develop not only against the blood stages parasites but also specific against sporozoites and the circumsporozoite protein (CSP). Results show that a single sporozoite inoculation does not induce antibodies, but that a single inoculation repeated every year would after 10 to 15 years at least induce detectable but low levels of sporozoite-specific antibodies. Conversely, multiple inoculations per year induce a strong humoral immune response within 2 years [20]. Immunoglobulins are associated with protection against malaria inoculation, by activating monocytes. The role of monocytes in malaria prophylaxis was first proposed by a research team from Uganda. Monocytes have a limited life span. In the absence of appropriate stimuli, they undergo apoptosis, but under

the influence of survival signals, these cells differentiate into macrophages or dendritic cells. It has been shown that ligation of IgE on human monocytes markedly reduces the apoptosis. A cooperative, synergistic effect between immunoglobulins and monocytes was demonstrated. The addition of monocytes from healthy individuals to *Plasmodium falciparum* cultures in the presence of serum from immune individuals markedly inhibits the proliferation of the parasite in vitro. The activity of monocytes alone and immunoglobulins alone was moderate and inconsistent [21,22]. Immunoglobulins protect efficiently by targeting α-gal on sporozoites immediately after inoculation by Anopheles mosquitoes; but not against the disease once the erythrocytic stage of malaria is established. IgE also interferes with the 14-3-3 ε protein during the invasion of hepatocytes by sporozoites. Antibodies are capable of blocking infection of the liver by Plasmodium falciparum. They could block infection at the pre-erythrocytic stage in several ways, either by neutralizing sporozoites directly, opsonizing sporozoites for phagocytosis or blocking invasion of sporozoites into hepatozoites [23-27].

In a mice model it was shown that prior exposure to saliva had no detectable effect on the rate of migration of the sporozoites away from the skin. The applicability of these results to humans remains to be confirmed as mice do not exhibit the typical wheal and flare reaction characteristic of humans [28]. The inhibition of sporozoites cell traversal activity seems to be an import element. The immunoglobulin 3D11 for example neutralizes 90% of the sporozoite infectivity by interacting with CSP. Circumsporozoite protein is the antigenic target of RTS, S and of other pre-erythrocytic malaria vaccines currently undergoing clinical trials [29,30]. A similar protection mechanism by IgE has been documented for leishmaniasis. IgE antibodies bind strongly to promastigotes [31]. It happens that Artemisia infusions are less efficient for non-immune Caucasians. It is probably not related to genetic strains, but to the absence of acquired immunity. In sub-Saharan Africa most people are almost continuously infected by *Plasmodium falciparum* parasites, and the majority of infected adults rarely experience overt disease. In naïve individuals *Plasmodium falciparum* infection is almost always symptomatic and clinical symptoms can be observed at very low parasitemia levels [32]. A study involving several African ethnic groups, some of Caucasian ascent, others of the negroid type, was unable to detect genetic factors able to explain the significant differences in immune response [33]. But in an Indian study no circulating free antibodies were detected in some individuals. The significance of this trait present in some individuals deserves to be studied in depth [34,35]. The total IgE level in a population is strongly related to the malaria endemicity in that area. In a study from the Uppsala University in Sweden it was found that the total level of IgE in the Swedish population was much lower at 8ng/ml than for adult donors from Liberia (2123 ng/ml), Madagascar (301ng/ml) and Thailand (647ng/ml), areas where malaria transmission and endemicity is high. None of the donors had malaria when blood was taken.

IgE titers are negatively correlated with gametocyte carriage and this may be an important factor in a area of high endemicity [36,37]. During stage II to V gametocytes hide in the bone marrow for their development. IgE is well present in the bone marrow; it is even generated there in case of stress (anemia, drugs, parasites, bacteria…). Also mast cells originate from a bone marrow progenitor and subsequently develop different phenotype characteristics locally in tissues. Mast cells play an important protective role, are involved in wound healing, immune tolerance, defense against pathogens and blood-brain barrier functions. These cells are known to accumulate at sites of inflammation in response to parasite and bacterial infections. There they degranulate and set free histamines, IgE and TNF-alpha. Degranulation is proportional to parasitemia, increasing from virtually 0 to 40% in the case of complicated malaria. It is difficult to understand why gametocytes hide in the bone marrow for their development. Mast cells express a high affinity for IgE. Often mast cells are coated with IgE [38-42]. Artesunate is antagonistic with the formation of IgE and its mechanisms of action against parasites [43,44]. Worse even, a 5-fold increase in gametocytogenesis in *Plasmodium falciparum* has been documented for chloroquine *in vitro* [45].

It is shocking to read in a recent paper that while chloroquine may significantly reduce mortality, but whether it will interfere with the host immune system is currently unknown. And the authors demonstrate in a mice model that a single dose of chloroquine soon after malaria infection significantly suppresses both the cellular and humoral immunity of the host. The authors conclude that chloroquine only is efficient in the well established erythrocytic stage by inhibiting hemozoin formation, but, if used in prophylaxis, may have dramatic impacts on the immune system and malaria prevalence [46]. This is not surprising as chloroquine reduces $CD4^+$ activation [47]. Is it criminal negligence not to have studied in the European Institutes of Tropical Medicine and elsewhere the impact of this inhibition of the immune system might have on prophylaxis and transmission and to have alerted the African communities against these risks. Chloroquine is still massively sold in Africa and the second most preferred medicine after ACTs (Artemisinin Combined Therapies).

Acknowledgement

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Conflict of Interest

None.

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