Reply to Eisenhut

To the Editor—In his recent letter, Eisenhut presents a hypothesis to explain the increased levels of IgG antibodies found in patients with cerebral malaria (CM), compared with other malaria patients, in a study conducted in Malawi [1]. In our study we could not rule out that differences in antibody levels were the result of differences in prior exposure.

It is proposed that elevated IgG levels could be explained by reduced clearance resulting from down-regulation of Fc receptors (FcR) induced by interleukin (IL)-4 in combination with tumor necrosis factor (TNF)–α, a cytokine that is elevated in children with CM [2]. The same explanation is suggested for elevated levels of immune complexes (IC) in CM patients [3].

Although this hypothesis is plausible, the role of cytokines in the pathogenesis of malaria is not fully elucidated and is probably very complex, possibly involving the coordinated effect of many immune mediators in addition to FcR, IL-4, and TNF-α. High concentrations of serum Th1-type proinflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-8, IL-2 soluble receptor, IL-12, and IL-18, in patients with severe falciparum malaria have been reported extensively previously [2, 4–9].

Our study did not measure plasma levels of IgE, IgG IC, IgE IC, or cytokines, and therefore we focused on the antibody findings and did not speculate about related cellular immune mechanisms that could also be associated with the differential IgG levels observed. The interpretations suggested here remain conjectural and would need to be tested in additional studies.

Elevated serum IgE in patients with CM suggest an underlying imbalance in favor of the Th2 cytokines IL-4 and/or IL-13, which are primarily responsible for isotype switching from IgM to IgE and IgG4 [10]. The interaction of antigen-IgE IC or of anti-IgE IgG with monocytes via FcεR might efficiently induce release of TNF-α and nitric oxide, both associated with CM and fatal outcome [2, 5, 11]. The production of Th1 cytokines is down-regulated by anti-inflammatory cytokines such as IL-10 [12] and transforming growth factor (TGF)–β [13], and an imbalanced TNF-α/IL-10 ratio or and inadequate IL-10 feedback response may contribute to the pathogenesis of severe malaria [14], CM [15] and severe malarial anemia (SMA) [16, 17]. Elevated levels of TNF-α and nitric oxide have also been implicated in the pathogenesis of SMA [18] as causes of dyserythropoiesis and erythropagocytosis [19]. Severity could be related to polymorphisms in the gene promoters associated with increased TNF-α [20] or with decreased IL-10 synthesis [21]. Interestingly, CM and SMA have been associated with different TNF-α promoter alleles [22]. IL-10 is also a growth and differentiation factor for activated human B cells, together with IL-4, promoting switching to IgG, IgA, and IgM isotypes [23]; IL-10 induces preferential production of IgG1 and IgG3, but not IgG2 or IgG4, in naive human B cells [24].

A different possibility that was not discussed in the article is that the presence of antibodies could have a disease-promoting role. For example, IC formation and deposition in the cerebral microvessels has been associated with CM in some studies [25, 26], but not in others [27]. It has also been proposed that IgG or IC could bind to uninfected erythrocytes and accelerate their spleen clearance by macrophages or complement-mediated lysis, thus contributing to SMA [28, 29]. To date, however, the immunological hypotheses for the pathogenesis of severe malaria remain unconvincing.

The pediatric autopsy studies conducted in Malawi provide an opportunity to investigate the possible deposition of IC and IgE in cerebral capillaries, its potential correlation with circulating IgG, IgE, IgG IC, or IgE IC, and the role that this might have in the pathogenesis of human CM.

References
Response to “Case of Yellow Fever Vaccine–Associated Viscerotopic Disease with Prolonged Viremia, Robust Adaptive Immune Responses, and Polymorphisms in CCR5 and RANTES Genes”

To the Editor—We read with interest Pulendran et al.’s article reporting a patient who, after vaccination for yellow fever, developed viscerotropic yellow fever disease due to disruption of the CCR5–RANTES axis [1]. CCR5, present on T cells and macrophages, is one of the key coreceptors for the entry of HIV into cells [1]. Recently, a new CCR5-receptor antagonist has been marketed and demonstrated to have potent anti-HIV activity [2].

Since the introduction of highly anti-retroviral treatment (HAART), HIV-infected persons can often live normal lives and will probably increasingly be able to travel to areas where yellow fever is endemic. The Centers for Disease Control and Prevention recommends that “persons who are HIV-infected but do not have AIDS or other symptomatic manifestations of HIV infection, who have established laboratory verification of adequate immune system function, and who cannot avoid potential exposure to yellow fever virus should be offered the choice of vaccination” [3]. According to the World Health Organization, “yellow fever vaccination can be considered for adults with HIV in WHO clinical stage 1 or 2, who have CD4 counts >200 cells/μL, if they are required to travel to an area where there is an epidemic of yellow fever or the disease is endemic” [4, p. 34–5]. In light of Pulendran et al.’s findings, it is possible that, despite having adequate immune function, persons with HIV infection who are receiving a HAART regimen containing a CCR5-receptor antagonist could be at particular risk of adverse events after being vaccinated for yellow fever. CCR5-receptor antagonists are not yet widely used in HAART programs in countries where yellow fever is endemic, but this may change. We propose that, for the moment, persons treated with these drugs should not be vaccinated for yellow fever.

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References


