Reduced Fc Receptor–Mediated Clearance as Explanation of Increased Antiplasmodial Antibody Levels in Cerebral Malaria

To the Editor—A recent study by Dobano et al. [1] investigated IgG antibody responses to conserved regions of merozoite proteins from Plasmodium falciparum in Malawian children with severe malaria and found that levels of antibodies to all antigens investigated were elevated in patients with cerebral malaria, compared with patients with uncomplicated malaria. The differences were not related to parasite density or patient characteristics relevant to previous exposure. Antibody levels decreased on recovery, supporting the idea that antibody levels did not reflect preexisting antibodies, but rather events occurring during the acute infection. The authors refer in the discussion to a study conducted by Troye-Blomberg et al. [2], which showed that production of interleukin-4 by activated human T cells is associated with elevated levels of serum antibodies to activating malaria antigens. The authors did not, however, provide an explanation of how this could explain the increased antibody levels.

Antibodies and immune complexes are cleared from the circulation after interaction of their Fc segment with Fc receptors on cell populations, including the mononuclear phagocyte system, mainly in the liver and spleen [3]. Receptors for IgG are categorized into subtypes hFcγRI, II, and III, which bind IgG subclasses with a high affinity for IgG 1 and 3 but not IgG 2 and 4 [4]. The expression of all 3 receptor types is down-regulated by interleukin (IL)–4. IL-4 acts synergistically with tumor necrosis factor (TNF) [5], a mediator elevated in children with cerebral malaria. Increased IL-4 levels may be an expression of the dominance of Th-2 cytokines in the pathogenesis of cerebral malaria, which is also evident from elevated IgE levels [6]. A reduction of the clearance of immunoglobulins by down-regulation of Fc receptors may explain the association of both increased immunoglobulin levels and circulating immune complexes [7] with cerebral malaria. Pathological deposition of immune complexes in cerebral capillaries may lead to local vasculopathy, similar to the phenomenon of glomerulopathy in systemic lupus erythematosus, another condition that involves reduced clearance of immune complexes [8]. Cerebral malaria was also associated with the deposition of IgE-containing immune complexes in cerebral capillaries [7]. In contrast to its effect on IgG receptors, IL-4 can up-regulate Fc receptors for IgE (FceRII) on macrophages, which—if cross-linked by IgE immune complexes—could lead to the release of TNF [9], a cytokine that leads to increased cytoadherence of parasitized red blood cells by up-regulation of intercellular adhesion molecule-1 in endothelial cells.

Future research needs to investigate the correlation between Fc receptor density on circulating monocytes and cerebral malaria and its severity. Stimulation of IgG Fc receptor expression in animal models of cerebral malaria (e.g., BALB/c mice, in which immunocomplex formation correlates with cerebral malaria [10]) with substances like zymosan [3] could be explored as a way to prevent cerebral malaria by reducing pathological immune complex deposition in the central nervous system.

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References

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