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Cerebral Malaria II. The Role of Tumor Necrosis Factor in its Pathogenesis

Abstract

Cerebral malaria (CM), a complication found in Plasmodium falciparum infection, is characterized by the presence of coma. It can be accompanied by hypoglycemia and lactic acidosis, that comprise major cause of death in 10-50% of CM cases. Conventional explanation that coma is due to obstruction of small blood vessels by trapping of parasitized red blood cells, that ends in ischemia and anoxia, does not fit to the facts that when the patients survived, only few sequels left and most of the sequels were transient. The first part of the literature review (Cerebral Malaria I) concluded that sequestration of red blood cells bearing old stages of P. falciparum in the vessels in the deep organs is started by cytoadherence of p-rbc to the endothelial cells lining blood vessels that involves the role of adhesion molecules. The expression of adhesion molecules on the surface of endothelial cells is stimulated by parasite antigen and up-regulated by cytokines especially TNF-α. Many reports have associated TNF-α with symptoms of malaria. Paroxysms or periodic attacks of fever in malaria was associated with schizont rupture that stimulated production of TNF-α, an endogenic pyrogen. And TNF-α overproduction was implicated with symptoms of severe malaria, including CM. The association has been confirmed by plenty of clinical data and TNF-α was also found in brain tissue from biopsy materials. CD4+ T (Th1) cells, which secretes IFN-γ, is needed to amplify and optimize TNF production. The role of TNF-α, TNFR and CD4+ T cells was confirmed by genetic findings and immunepidemiologic studies. Some investigators proposed the role of NO in CM. Local NO overproduction, associated with the effects of TNF-α, IFN-γ, malaria antigen and partial hypoxia caused by sequestration, was supposed to interfere normal neurotransmission leading to altered consciousness and coma. This NO theory can explain the occurrence of transient coma and minimal sequelae when patients recovered. While severe hypoglycemia, lactic acidosis, anoxia and ischemia caused by complete occlusion of local blood vessels can be associated with fatal outcomes and permanent organ dysfunctions. Analysis of parasite antigen which stimulates TNF-α production and to use the antigen to stimulate production of blocking antibody could be one way to cope the problem of CM and other symptoms of severe malaria. Trials and research on the use of anti-TNF antibody, corticosteroids and pentoxiphylline, and analysis of the effects of conventional antimalarials on TNF-α and NO production has been done, but the results were still inconclusive. The possible use of PEMP1 and other parasite ligands involved in cytoadherence has been written in the first part of review. Further research and efforts are still needed until the results can be used in practice.

Keyword: cerebral, malaria, TNFα, CD4+ T, adhesion, molecules, nitric, oxide,

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