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Can neuronal damage be related to blood brain barrier activation? What can we learn from Cerebral Malaria?

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Plasmodium falciparum is the etiological agent in malaria. Especially in children, exposed non immune travelers and military personnel malaria can lead to serious symptoms, including cerebral malaria (CM). Clinically, CM includes seizures, reversible coma and often death. Upon clearance of the infection, patients are often left with neurologic sequelae, such as seizures, learning and behavioral disorders. Recent data also show that ADHD can be linked to CM. Post malaria syndrome can also include psychotic or acute confusional episodes and tremor. In CM Plasmodium infected erythrocytes (PRBC) sequester into high endothelial venules in close contact with the blood brain barrier (BBB) endothelium. This sequestration occurs without invasion into the brain, still coma and seizures are characterizing CM. It is unclear as to how these parasites, inside an infected PRBC and confined to the brain vasculature induce neurological dysfunction. In CM, the BBB lies at the interface of the events occurring in blood and brain. The BBB is part of the neurovascular unit (NVU), a concept that emphasizes homeostatic interactions between its components to ensure optimal functioning of the central nervous system. It is hypothesized that activation of the BBB endothelium disturbs the homeostasis between the astro-glial and neuronal components of the NVU leading to neurological dysfunction. We constructed an in vitro model of the human BBB and exposed this to PRBC. This resulted in increased ICAM-1 expression on the cells and decreased the integrity (barrier function) of the monolayers in a dose dependent manner. Microarray and Gene Ontology (GO) analysis indicated a predominance of the NF□B mediated proinflammatory responses among the host signaling pathways. RT-PCR and protein analysis confirmed the increase in transcripts and release of cytokines and chemokines. To assess whether BBB secretions could affect the brain, BBB models were constructed on TW inserts. Upon confluence, TW-BBB models were placed in the Cellscope and exposed to PRBC. Media was collected from the basal side of BBB models and added to astroneuronal cultures. These basal secretions caused dose-dependent abnormal astroneuronal morphology and cell death. Determination of the underlying pathogenesis of observed BBB activation and astroneuronal effects may lead to development of adjunctive neurotherapeutics to ameliorate neurologic sequelae.

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