Characterizing the Relationship of Histidine-Rich Protein-2 to the Neurologic Sequelae of Severe Malaria

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ABSTRACT

Despite improvements in malaria control and diagnostics, severe malaria continues to claim 800,000 lives every year. Plasmodium falciparum, the parasite that most often causes the severe forms of malaria, detoxifies its internal environment in the red blood cell stage of infection through a process mediated by the parasite-secreted histidine-rich protein 2 (pHRP2). pHRP-2 is widely used in diagnostics, yet its role in severe malaria is not well defined.

Therefore, this project aimed to characterize the relationship of pHRP2 to the neurologic sequelae of severe malaria. My hypothesis was that pHRP2 levels would be significantly higher in children with severe disease, as compared to healthy controls and that higher levels would be associated with neurologic sequelae.

METHODS

Malaria is a complex and life-threatening disease that claims approximately 800,000 lives every year. Five different Plasmodium species cause malaria in humans, the most dangerous being Plasmodium falciparum. P. falciparum infections can lead to severe disease defined by presence of the parasite and either coma in cerebral malaria (CM) or severely low hemoglobin levels in severe malarial anemia (SMA) [1]. The burden of severe malaria is not only the loss of life, but also neurologic deficits, as well as recurrent severe anemia [2] [3]. While numerous studies have investigated severe malarial pathogenesis, the mechanism remains undefined, though it is hypothesized to involve infected erythrocyte sequestration in post-capillary venules of the brain, cytokine mediated inflammation, and hemostasis dysfunction [4].

Plasmodium parasites invade and replicate in host red blood cells, metabolizing red cell hemoglobin as its major energy source for growth and replication [4]. In metabolizing hemoglobin, the toxic byproduct heme is created. To survive, Plasmodium detoxifies heme into hemozoin, a process that is mediated in part by the parasite-secreted histidine-rich protein-2 (pHRP-2) [5]. Thus, there is a direct correlation between pHRP-2 concentration and number of parasites in the body, including parasites both in peripheral blood and those sequestered in tissues. Subsequently, pHRP-2 is widely used as a biomarker in commercially available malaria rapid diagnostic tests as it is a more accurate measure of parasite biomass as compared to blood smears [5]. Furthermore, sequestration of erythrocytes is associated with more severe disease and therefore high levels of pHRP2 may indicate a greater amount of sequestration.

RESULTS

**pHRP2 Levels in Cerebral Malaria**

CM samples had the highest median pHRP2 concentration (24,864 ng/ml) followed by SMA (7590 ng/ml) and then community controls (48 ng/ml). pHRP2 levels between all three groups (CM, SMA, and CC) were found to be statistically significant (p = 0.001).

A significant difference was also found in pHRP2 levels between those who survived and died from cerebral malaria with increased pHRP2 levels seen in fatal cases (p = 0.020).

pHRP2 levels were significantly higher in patients who were retinopathy positive compared to those who were retinopathy negative (p = 0.02).

pHRP2 concentrations were also compared to the presence of neurologic deficits and the duration of coma, but no statistical significance was found.

REFERENCES


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