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New findings highlight the role of endothelial cell activation in children with cerebral malaria

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Researchers have identified a novel pathway that may contribute to the high mortality associated with severe malaria in sub-Saharan African children. The study, published March 20 in the open-access journal *PLoS Pathogens*, reports that severe Plasmodium falciparum infection results in disruption of the endothelium, causing release of ultra-large von Willebrand factor (VWF) protein. Together with reduced levels of VWF-specific cleaving enzyme ADAMTS13, this finding may contribute to our knowledge of the pathophysiology of malaria.

Severe *P. falciparum* malaria is responsible for an estimated 1 million deaths each year in sub-Saharan African children. In spite of this significant mortality, the mechanisms underlying the clinical development of severe malaria remain poorly understood. However, studies have shown that red blood cells (erythrocytes) infected with malaria parasites can adhere to the inner lining (endothelium) of small blood vessels. In this study, an international group of researchers, led by Dr. James O'Donnell of Trinity College Dublin, investigate the significance of this interaction between the infected erythrocytes and the blood vessel wall.

Over a one-year period, the group studied children under six years with severe *P. falciparum* malaria at the Komfo Anokye hospital in Kumasi, Ghana. In blood samples from these children, the researchers found that plasma levels of a specific adhesive protein, VWF, were markedly

increased. The VWF protein is synthesized within endothelial cells, and plays a critical role in tethering circulating blood cells to the vascular wall at sites of injury. In order to prevent excessive blood clot formation, VWF activity in the blood is normally tightly regulated by ADAMTS13. In the Ghanaian children, the plasma levels of this important enzyme were also found to be significantly reduced.

Thus, severe *P. falciparum* infection causes disruption of the endothelium, resulting in the release of large amounts of VWF into the blood. Moreover, this VWF protein cannot be inactivated due to a concurrent decrease in plasma ADAMTS13 enzyme levels. Further studies will be required to define the role played by the abnormal, highly adhesive VWF in mediating the critical small-vessel obstruction associated with severe malaria. Nevertheless, these findings shed new light on the mechanisms underlying the interaction between the malaria parasite and its human host, and are not only of scientific interest, but may also create future new therapeutic opportunities for these children.

More information: Larkin D, de Laat B, Jenkins PV, Bunn J, Craig AG, et al. (2009) Severe Plasmodium falciparum Malaria Is Associated with Circulating Ultra-Large von Willebrand Multimers and ADAMTS13 Inhibition. PLoS Pathog 5(3): e1000349. doi:10.1371/journal.ppat.1000349, dx.plos.org/10.1371/journal.ppat.1000349

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