THE FASEB JOURNAL
The Journal of the Federation of American Societies for Experimental Biology

Glycocalyx breakdown is increased in African children with cerebral and uncomplicated falciparum malaria

Tsin W. Yeo , Peggy A. Bush , Youwei Chen , Sarah P. Young , Haoyue Zhang , David S. Millington , Donald L. Granger , Esther D. Mwaikambo , Nicholas M. Anstey , J. Brice Weinberg

First published: 26 October 2019

https://doi.org/10.1096/fj.201901048RR

Abstract

Cerebral malaria (CM) from *Plasmodium falciparum* infection is associated with endothelial dysfunction and parasite sequestration. The glycocalyx (GCX), a carbohydrate-rich layer lining the endothelium, is crucial in vascular homeostasis. To evaluate the role of its loss in the pathogenesis of pediatric CM, we measured GCX degradation in Tanzanian children with World Health Organization-defined CM (n = 55), uncomplicated malaria (UM; n = 20), and healthy controls (HCs; n = 25). Urine GCX breakdown products [glycosaminoglycans (GAGs)] were quantified using dimethylmethylene blue (DMMB) and liquid chromatography-tandem mass spectrometry assays. DMMB-GAG and mass spectrometry (MS)-GAG (g/mol creatinine) were increased in CM and UM compared with HCs ($P < 0.001$), with no differences in DMMB-GAG and MS-GAG between CM and UM children or between those with and without a fatal outcome. In CM survivors, urinary GCX DMMB-GAG normalized by d 3. After adjusting for disease severity, DMMB-GAG was significantly associated with parasitemia [partial correlation coefficient (P_{corr}) = 0.34; P = 0.01] and plasma TNF (P_{corr} = 0.26; P = 0.04) and inversely with plasma and urine NO oxidation products [P_{corr} = -0.31 (P = 0.01) and P_{corr} = -0.26 (P = 0.03), respectively]. GCX breakdown is increased in children with falciparum malaria, with similar elevations in CM and UM. Endothelial GCX degradation may impair endothelial NO production, exacerbate adhesion-molecule expression, exposure, and parasite sequestration, and contribute to malaria pathogenesis.