The brain-kidney-retinal axis in severe falciparum malaria

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Keywords: cerebral malaria, brain, renal failure, retina

We would like to thank Burke *et al.,* for their interest in our article on the brain-kidney axis in severe malaria [1] and for outlining the striking similarities between the kidney and the eye in terms of blood supply and vulnerability to microvascular disease [2]. As studies have shown the retina is a window to the pathological changes in the brain of children with cerebral malaria [3], retinal investigations are a powerful tool that should be leveraged when evaluating the kidney-brain axis.

In fact, there are data supporting the kidney-brain-retinal axis in severe malaria. Acute kidney injury (AKI) is a risk factor for both blood-brain-barrier disruption as well as the presence and severity of retinopathy [4]. Specifically, in children with cerebral malaria, AKI was associated with peripheral and macular whitening and the presence and severity of retinal hemorrhages [4]. The kidney, brain, and retina are connected by the endothelium monolayer that maintain tissue perfusion and vascular tone. Endothelial populations are both dynamic and diverse, with markers of endothelial activation associated with AKI, brain injury [5], and retinopathy.

The angiopoietin-Tie-2 system is an important regulator of endothelial activation. Endothelial receptor tyrosine kinase (TEK) or Tie-2 binds to ligands angiopoietin-1 (Angpt-1) or Angpt-2 to regulate endothelial activation. The Angpt-Tie-2 pathway lies at the interface between inflammation and angiogenesis. Angpt-1 promotes vessel integrity while Angpt-2 is a functional antagonist and promotes vessel destabilization, sensitizes cells to inflammatory responses and can lead to vascular leak and apoptosis [6].

Angpt-2 is a well-established marker of AKI in critical illness, including malaria [5,7]. Angpt-2 is elevated in pediatric cerebral malaria, and is associated with retinopathy severity including the number of retinal hemorrhages, as well as the extent of retinal whitening and vessel color changes [8]. These findings are consistent with studies in patients with sepsis where an Angpt-2 gene variant (rs2920656C > T) associated with lower Angpt-2 protein levels was associated with a less severe sub-phenotypes of AKI [9]. Perturbations in the Angpt-Tie-2 pathway have been implicated in multiple forms of retinopathy [10,11] and polymorphisms in the *ANGPT2* gene have also been implicated in retinopathy (rs2442598 G>A) [12]. Based on these findings, there is a strong reason to believe that malaria will impact choroidal thickness in children, as proposed by Burke *et al.,* and studies should investigate the relationship between the Angpt-2-Tie-2 axis as it relates to the kidney, brain, and retina.

Lastly, it is noteworthy that the strong association described between retinal changes and cerebral malaria in children is not clear in adults. In the latter category, retinopathies are also seen in uncomplicated and severe non-cerebral malaria [13]. This may result from age-specific differences in cerebral malaria pathophysiology [14]. A more likely explanation is that the current definition of cerebral malaria in adults is inadequate, as evidenced by the recent report of cerebral malaria-specific MRI signatures in severe malaria patients without coma [15]. MRI approaches to identify cerebral involvement and potentially microhemorrhages, coupled with retino-choroidal assessments, are warranted to rigorously examine similar correlations between brain and eye changes in adult patients,

as well as their subsequent use in exploring the brain-kidney pathogenic axis during severe malaria in this age group.

Acknowledgments

ALC is supported by National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH) under award numbers R01AI165946 and 5R21AI151349-02, the National Institute of Neurological Disorders and Stroke under award number R01NS055346, and the Ralph W. and Grace M. Showalter Research Trust Award. DD is supported by the National Institute of Neurological Disorders and Stroke under award numbers R21NS127215 & R21NS129234, and R01NS055346. SCW is supported by the National Institute of Allergy and Infectious Diseases of the NIH under award number U19AI089676, and the Medical Research Council UK under award number MR/S009450/1. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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