Short Report

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Short Report: Reversibility of Retinal Microvascular Changes in Severe Falciparum Malaria

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Abstract. Malarial retinopathy allows detailed study of central nervous system vascular pathology in living patients with severe malaria. An adult with cerebral malaria is described who had prominent retinal whitening with corresponding retinal microvascular obstruction, vessel dilatation, increased vascular tortuosity, and blood retinal barrier leakage with decreased visual acuity, all of which resolved on recovery. Additional study of these features and their potential role in elucidating the pathogenesis of cerebral malaria is warranted.

The pathogenesis of coma in falciparum malaria and its rapid reversibility are potential targets for adjunctive therapies, but they are not well-understood. Microvascular obstruction is probably an important contributor. The brain microvasculature is relatively inaccessible; it can be studied in detail only at post-mortem. Similarly, microvascular obstruction in the retina is thought to be a major contributor to the unique retinopathy of severe falciparum malaria, and, because it is easily visualized in living subjects, in-depth study is providing new and valuable insights. We describe an adult patient with cerebral malaria who had prominent retinal changes with some previously unrecognized features that resolved on recovery.

A 24-year-old male truck driver from Orissa, India was admitted with severe Plasmodium falciparum malaria (parasitemia = 0.3%) with coma, generalized convulsions, hyperlactatemia, renal failure, and black urine. He had no prior medical history. Retinal photography showed bilateral patchy macular whitening with corresponding capillary non-perfusion and leakage of fluorescein caused by blood retinal barrier breakdown on fluorescein angiography (Figure 1). He was treated with intravenous artesunate, and from recovery of consciousness on day 3 to discharge, his visual acuity was marked reduced (counting digits only), with loss of red–green color vision. Repeat examination on day 55 showed that the retinal changes, angiogram abnormalities, and visual deficits had resolved (acuity 6/9 bilaterally and normal color vision). Although increased vascular tortuosity has not been well-described in malaria, it is a recognized feature of other vascular occlusive diseases of the retina. Vessel tortuosity is caused by a combination of vessel dilation from radial stretching and the vessel taking a more serpentine path because of longitudinal stretching. Several pathogenic mechanisms have been proposed for increased retinal vascular tortuosity. They include (1) increased blood flow in anemia, (2) early angiogenesis caused by ischemia or inflammation and (3) dysregulation of vascular tone caused
by microvascular obstruction and relative hypoxia in diabetic retinopathy, and (4) venous congestion causing elevated vascular pressure and dilatation of blocked vessels in CRVO and raised intracranial pressure resulting in central retinal vein compression. In malaria, anemia is common, uninfected red blood cells have reduced deformability, and sequestered parasites cause microvascular and venular obstruction. Angiogenesis is probably unimportant over the short timescale.1

Increased vascular tortuosity has not been well-described previously in severe falciparum malaria, possibly because the normal appearance of retinal vessels varies significantly between individuals and subtle changes are difficult to identify. Ophthalmoscopy revealed engorgement and tortuosity of retinal veins in 26% of children with cerebral malaria in Ghana, which mostly resolved by 1 week.8 In our patient, comparison of retinal photographs provided a more objective measure. Means of quantifying vessel tortuosity using computer-aided image processing are under development.

The angiogram in this patient showed focal leakage of fluorescein across the blood–retinal barrier (BRB) in areas of non-perfusion, suggesting a common etiology. The BRB is analogous to the blood–brain barrier, which is also mildly disrupted in cerebral malaria. Leakage from larger retinal vessels crossing ischemic areas is a well-known phenomenon in retinal ischemia. The significance of this finding as a contributor to the pathogenesis of malarial coma is not known. More angiographic studies are needed.

This patient had decreased visual acuity, which had resolved at follow-up. Although it is not possible to give a cause, it is the first report of an association between macular retinal whitening and decreased visual acuity with subsequent recovery.

Additional studies of malarial retinopathy have great potential to enhance our understanding of vascular changes in severe malaria. To maximize their impact, studies should use retinal photography, where possible, to allow detailed examination of the full range of fundus signs by multiple blinded observers. This examination should be done both acutely and at follow-up. Fluorescein angiography provides a highly detailed map of CNS retinal perfusion. There is a need for additional detailed studies to include assessment of vascular tortuosity to investigate its role as a potential early and sensitive marker in studies of severe malaria.

The rate of reversibility of malarial retinopathy has potential as an end point in intervention studies of severe malaria, particularly for adjunctive therapies that directly target the pathogenesis. Additional information on the speed of reversibility of the various components of malarial retinopathy is needed, and studies are underway to investigate this.

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REFERENCES


