Dear Sir:

A recent study reported that retinopathy is a characteristic feature of cerebral malaria caused by *Plasmodium falciparum*. Severity of retinopathy was related to risk of death and duration of coma in survivors. One characteristic feature of malaria related retinopathy were hemorrhages, which were present in 46% of patients with cerebral malaria. A previous study showed that the number of retinal hemorrhages correlated with the number of cerebral hemorrhages.

Recently, a case of dietary folate deficiency associated with bilateral retinal hemorrhages was reported, which confirmed previous similar observations. Congenital folate deficiency due to a homozygous mutation in the methylenetetrahydrofolate reductase (MTHFR) gene has been associated with cerebral hemorrhages. Folate levels were significantly lower in patients homozygous for this mutation and cerebral hemorrhages compared with patients without and controls. An investigation of serum and cerebrospinal fluid (CSF) folate levels in patients with cerebral malaria showed significantly reduced levels compared with controls. After successful treatment of the acute malaria episode, CSF folate levels increased significantly. This may indicate that folic acid deficiency is involved in the pathogenesis of retinal and cerebral hemorrhages in cerebral malaria. The mechanism by which folic acid deficiency causes retinal and cerebral hemorrhages in malaria does not seem to involve anemia, which in itself is a well-established cause of retinal hemorrhages regardless of the etiology of anemia. Patients with retinal hemorrhages in cerebral malaria had the same packed red blood cell volume compared with patients with cerebral malaria without retinal hemorrhages, and patients with severe malarial anemia in another study had less severe retinopathy compared with patients with cerebral malaria. Electron microscopic studies of cerebrovascular endothelium in folate-deprived rats showed cytoplasmic swelling and mitochondrial degeneration in the endothelium and degenerative changes in the cerebrocortical microvascular wall, which may predispose to hemorrhages.

Future research needs to investigate an association of folate deficiency and MTHFR gene polymorphisms with retinal hemorrhages and disease severity in cerebral malaria.

REFERENCES


MICHAEL EISENHUT
Luton and Dunstable Hospital
Lewsey Road
Luton LU40DZ, United Kingdom
Telephone: 44-804-5127-0127
E-mail: Michael_eisenhut@yahoo.com

Dear Sir:

We thank Dr. Eisenhut for his interest in our review of malarial retinopathy and for suggesting the hypothesis that reduced folate levels may contribute to the production of retinal hemorrhages in cerebral malaria. Retinal hemorrhages are one component of malarial retinopathy, the other main ones being retinal whitening, vessel changes, and papilledema.

The morphology of retinal hemorrhages is different in the two conditions. The retinal hemorrhages seen in folate deficiency are multiple blot and flame hemorrhages. In cerebral malaria, the retinal hemorrhages are predominantly white-centered round hemorrhages, similar to Roth spots. In cerebral malaria the retinal hemorrhages, and the typical cerebral ring hemorrhages, often have fibrin thrombi in the small vessel at their center. It therefore seems unlikely that folate deficiency has a central role in the pathogenesis of retinal hemorrhages in cerebral malaria, although further research would be necessary to establish this.

We would like to clarify the relationship between anemia and cerebral malaria. Within the group of patients with strictly defined cerebral malaria (including severe anemia), the number of retinal hemorrhages correlates to the degree of anemia. However, within the group defined as severe malarial
anemia (excluding cerebral malaria), there are far fewer retinal hemorrhages. The pathogenesis of retinal hemorrhage in cerebral malaria seems to be associated with the presence of coma, and only then anemia. Because Olumese and others used fundoscopy through undilated pupils, they would have only been able to see a small proportion of the total number of retinal hemorrhages present in the patients they studied.

Given the presence of sequestered parasitized red blood cells, vessel endothelial changes, and hematologic derangement in cerebral malaria, there are many predisposing factors for retinal and cerebral hemorrhage.

REFERENCES


