The Eyes Have It: findings in the optic fundus correspond to cerebral pathology in fatal malaria

Blantyre Malaria Project and Malawi/Liverpool/Wellcome Trust Research Programme
Dept of Paediatrics
College of Medicine and Queen Elizabeth Central Hospital
Blantyre, Malawi

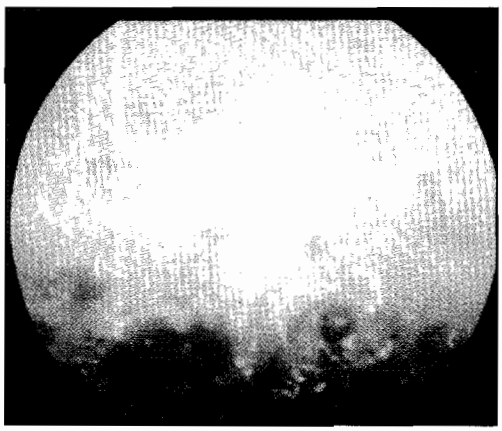
When *P falciparum* asexual parasites become mature, they are no longer seen circulating in the peripheral blood, because the red cells in which they have developed adhere to the endothelial linings of deep capillaries and venules. Mature parasites therefore become sequestered in microvascular beds in various organs, including the brain. Embryologically, the eye is an extension of brain tissue, and the eye contains one of the few capillary networks that can be directly observed in life.

In 1992, Dr. Susan Lewallen began examining the optic fundi of children admitted to the Malaria Project research ward in Blantyre. Using eye drops to dilate the eyes fully, she carried out detailed observations, using both a *direct ophthalmoscope* (which provides a great deal of magnification) and an *indirect ophthalmoscope*, which allows a three-dimensional view of the fundus. Dr. Lewallen and others, including Dr. Simon Harding from the University of Liverpool, described a 'malaria retinopathy' (1). It consists of four features, two of which are unique to malaria, and two of which are independently associated with a poor outcome:

Papilloedema: This swelling of the optic disk represents raised intracranial pressure, generally due to brain oedema. It is seen in 8-10% of patients with cerebral malaria, and when present, is associated with a 6-7 fold increase in the relative risk of death (2)

Haemorrhages: Haemorrhages, 50% of which may be white-centred, are seen in 35-40% of patients with severe malaria (Fig 1a.)

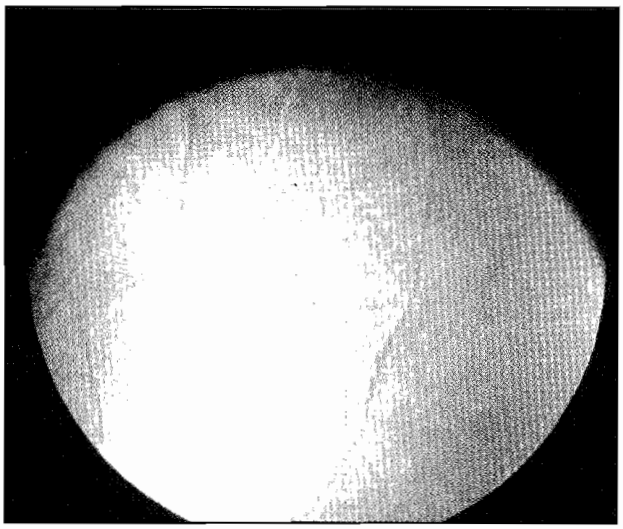
(Fig 1a.). *A fundus photo showing the characteristic retinal haemorrhages in a child with cerebral malaria. Some of the haemorrhages are white-centred.*



However, neither the number nor the evolution of haemorrhages is an independent predictor of a worse outcome (2).

Vessel changes: In 25% of patients with cerebral malaria, white or orange vessels can be observed in the optic fundi. This finding is unique to cerebral malaria. Often, only a single segment of a vessel will be affected, and frequently, the phenomenon begins at a branch point (Fig 1b).

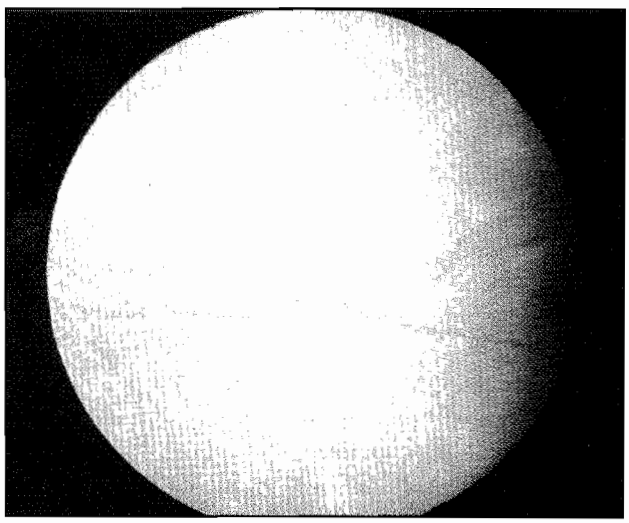
(Fig 1b). *This fundus photograph captures abnormal vessels. Notice the orange delineation of the branched vessel in the left/centre and upper part of the photo.*



Vessel changes are strongly associated with a poor outcome, but are not independent predictors (2).

Retinal whitening: Also unique to severe malaria, whitening occurs in about 50% of patients, most commonly in the macula. It does not cross blood vessels and often has a 'mosaic-like' appearance (Fig. 1c).

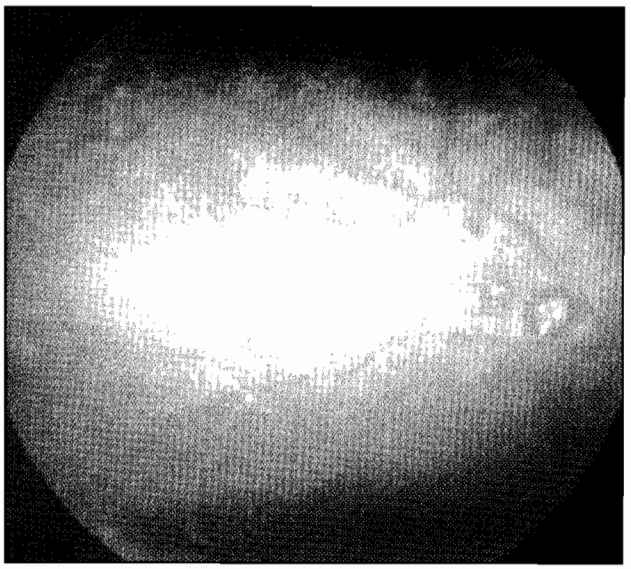
(Fig. 1c. *A mosaic of extra-macular whitening is evident in this fundus photograph.*).



It is an independent predictor of mortality, and cerebral malaria patients with whitening are three times more likely to die than are patients without (2).

Since 1996, a study of the clinicopathological correlates of fatal malaria has been underway in Blantyre, and to date, 65 autopsies have been completed. From these, we have been able to determine the relationship between the features of the malaria retinopathy during life, and pathological findings in the brain at the time of autopsy.

(Fig. 2a. *Retinal haemorrhages, abnormal vessels and whitening are all present in this patient.*)



The number of haemorrhages observed in the optic fundus during lifecorrelates significantly both with those seen in retinal histology and with those seen in the brain (3) (Figs 2b, 2c, 2d).To date, cerebral haemorrhages have only been detected in patients who had retinal haemorrhages during life.

Fig 2b. *At autopsy, the haemorrhages were easily seen in the white matter of the cerebral hemispheres (no magnification)*

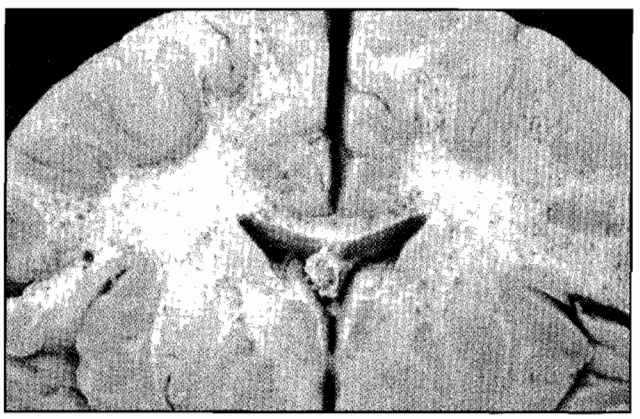


Fig 2c. *Cerebellar haemorrhages were present in the same patient, shown here in a thin section viewed under the low power of the microscope (H&E stained).*

Fig 2c.

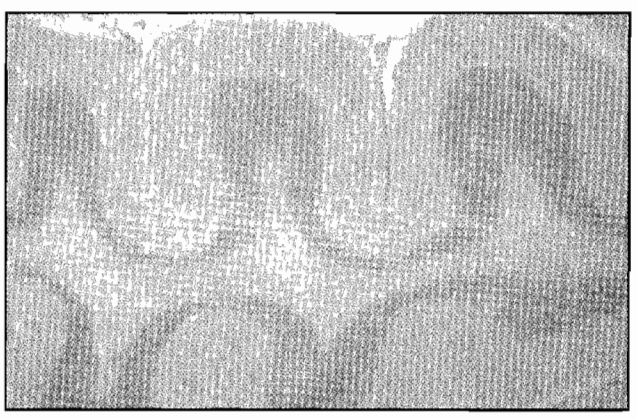
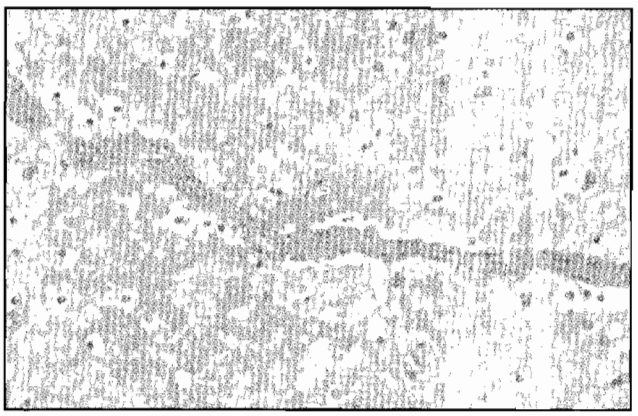
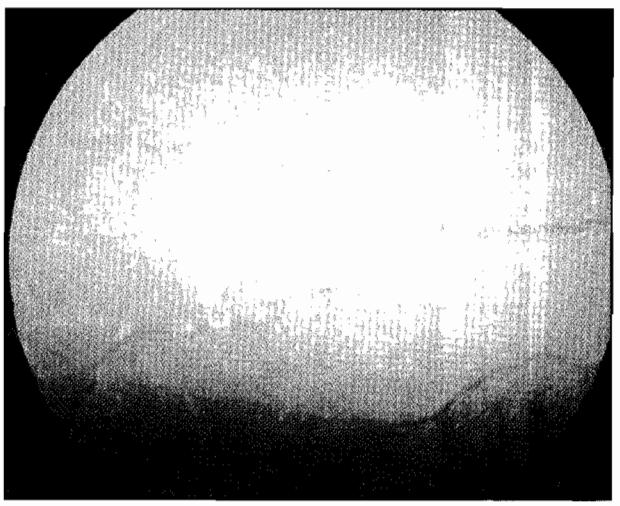


Fig 2d. *Both the brain and retinal haemorrhages are typically "ring haemorrhages", in which unparasitised red cells escape into the brain parenchyma, usually surrounding a vessel in which a fibrin thrombus has formed.*



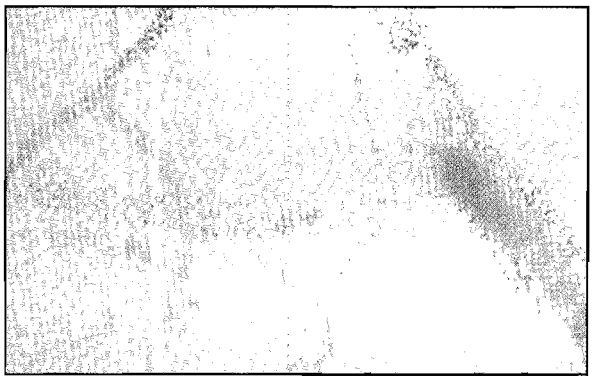
This abnormal optic fundus demonstrates segmental whitening in many vessels.)

Fig 3a.



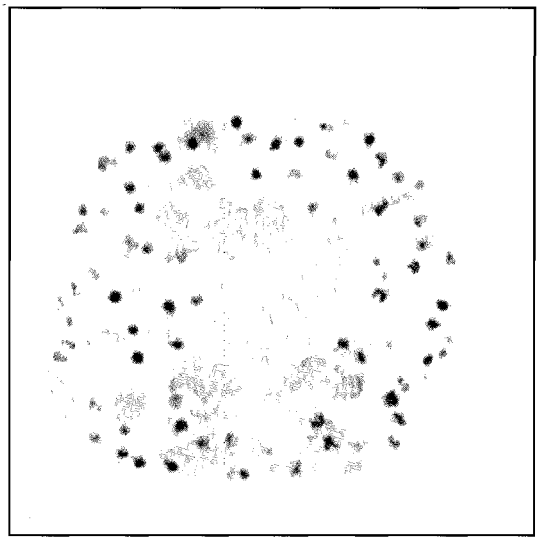
Colour changes in the retinal vessels (from red to orange or white, (Fig 3a)reflect the presence, in the vessel, of red cells containing mature, pigmented *P. falciparum* parasites (4). Pigment represents the by-product of haemoglobin degradation. Haemoglobin in solution in the erthrocyte cytoplasm is responsible for the red colour of a red blood cell. The malaria parasite, using a series of proteases, systematically degrades haemoglobin, salvaging the amino acids, and detoxifying the haeme. The haeme is safely packaged into haemozoin, which is also known as malaria pigment. The parasitised red cells which contain parasites mature enough to have produced haemozoin have less haemoglobin in solution, and thus are less red. Histologic examinations of the optic fundi (either as whole mounts (Fig 3b. or as tissue sections (Fig 3c.)

Fig 3b. *In this photomicrograph of a flat section of retina, the irregular distribution of parasitised, pigmented red cells can been seen. The parasitised red cells have less haemoglobin, and thus appear paler.*



This photomicrograph shows a central core of well-haemoglobinised red cells surrounded by pale, parasitised red cells containing little haemoglobin.))

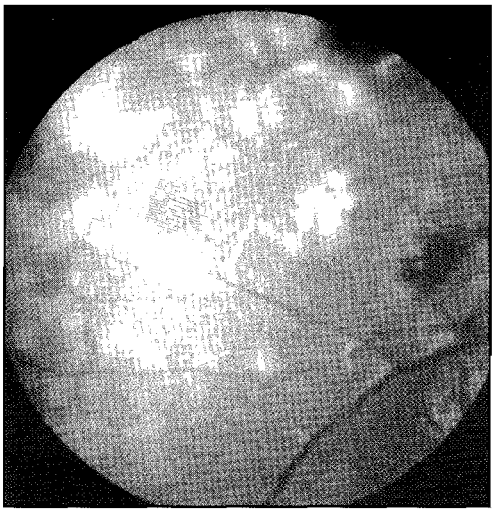
Fig 3c.



demonstrate that vessels which are orange or white upon funduscopic examination during life are the same vessels which contain dehaemoglobinized red blood cells and mature, pigmented parasites. There is a statistically significant correlation between the predominant stage of parasites in the optic fundi, and the predominant stage of parasites in the brain. In essence, the vessel changes visible in the optic fundus reflect the sequestration of parasitised red cells in the brain.

A detailed examination of the optic fundus, through fully dilated pupils, can reveal findings that reflect the various cerebral pathologies of fatal malaria.

(Fig.4. *This fundus photo captures three of the four distinguishing features of the malaria retinopathy: haemorrhages, retinal whitening, and vessel changes (segmental)).*



If adjunct therapies are developed to address the different processes involved, funduscopic examination may help to direct the choice of treatments. In the meantime, it can help to "fine tune" the clinical diagnosis of cerebral malaria.

References

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2. Lewallen S, Bakker H, Taylor TE, Wills BA, Courtright P, Molyneux ME. Retinal find ings predictive of outcome in cerebral malaria. Trans Roy Soc Trop Med Hyg 1996;90:144-146.

3. White VA, Lewallen S, Beare N, Kayira K, Carr RA, Taylor TE. Correlation of retinal haemorrhages with brain haemorrhages in children dying of cerebral malaria in Malawi. Trans Roy Soc Trop Med Hyg 2001;95:1-4.

4. Lewallen S, White VA, Whitten RO, Gardiner J, Hoar B, Lindley J, Lochhead J, McCormick A, Wade K, Tembo M, Mwenechanya J, Molyneux ME, Taylor TE. Clinical-histopathological correlation of the abnormal retinal vessels in cerebral malaria. Arch Ophthalmol 2000:118:924-928.