Visual outcomes in children in Malawi following retinopathy of severe malaria

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Aim: To investigate whether retinal changes in children with severe malaria affect visual acuity 1 month after systemic recovery.

Methods: All children with severe malaria admitted to a research ward in Malawi during one malaria season were examined by direct and indirect ophthalmoscopy. Visual acuity was tested in those attending follow up by Cardiff cards, Sheridan-Gardiner single letters, or Snellen chart.

Results: 96 (68%) children attended follow up, of whom 83 (86%) had visual acuity measured. Cardiff cards were used in 47 (57%) children, and Sheridan-Gardiner letters or Snellen chart in 29 (35%). There was no significant difference in the mean logMAR visual acuity between groups with or without macular whitening (0.14 versus 0.16, p = 0.55). There was no trend for worse visual acuity with increasing severity of macular whitening (p = 0.52) including patients in whom the fovea was involved (p = 0.32). Six (4.2%) children had cortical blindness after cerebral malaria, and all six had other neurological sequelae. Ophthalmoscopy during the acute illness revealed no abnormalities in four of these children.

Conclusion: Retinal changes in severe malaria, in particular macular whitening, do not appear to affect visual acuity at 1 month. This supports the hypothesis that retinal whitening is due to reversible intracellular oedema in response to relative hypoxia, caused by sequestered erythrocytes infected by Plasmodium falciparum. Impaired visual functioning after cerebral malaria is not attributable to retinal changes and appears to be a cortical phenomenon.
RESULTS
In all, 162 children were examined by funduscopy during the study period, and 20 (12%) died; 143 had cerebral malaria, seven had severe anaemia, and 12 had severe malaria alone. Ninety six (68%) survivors attended for follow up, of whom 83 (86%) were sufficiently cooperative for visual acuity testing, and form the basis for the remaining analysis.

The median age was 3 years and 4 months (interquartile range 22–60 months), and there were 44 (53.0%) females. Seventy nine of the patients had cerebral malaria, three had severe malarial anaemia and one had severe malaria alone. Fundus signs of severe malaria were present in 38 (46%) while in hospital, including 31 (37%) with macular whitening.

Visual acuity at follow up
The visual acuity was measured at a median of 27 days (interquartile range 22–29 days) after discharge. Cardiff cards were used for testing 47 (57%) children, Sheridan-Gardiner single letters for 18 (22%), Snellen chart for 11 (13%), including seven (8%) using a matching card, and the method used was not recorded for two children. Lea symbols were trialled on a number of patients, and were the only record of vision for one. Four children with persistent neurological sequelae could only be assessed according to their ability to fix and follow.

The measured visual acuities for different degrees of macular whitening are shown in figure 2. The difference in the mean logMAR acuities between children who had macular whitening (0.14) and those who had not (0.16) was not significant (p = 0.55). Similar results were obtained for children with foveal whitening (p = 0.70). There were similar proportions with visual acuity of better than 6/12 in groups with and without macular whitening (χ², p = 0.60).

There was no trend of worsening visual acuity with increasing severity of macular or foveal whitening (p = 0.52 and p = 0.32 respectively). Figure 3 shows the maculae of two patients with moderate macular whitening whose acuity was recorded as 6/12 and 6/9 4 weeks after discharge. Peripheral whitening, vessel changes, and capillary whitening were not associated with poor visual acuity at follow up. Four (4.8%) patients had papilloedema, none had neurological sequelae, and all had a visual acuity of 6/6 or 6/7.5 recorded at follow up.

DISCUSSION
Our study did not identify any loss of visual acuity attributable to retinal changes in children identified during their acute episode of malaria. Of the retinal signs in severe malaria, macular whitening might be expected to cause visual deficit as it is centred on, and often involves, the fovea. Other distinct features of retinopathy in malaria mostly affect the peripheral fundus. Macular whitening is a patchy opacification and thickening of the inner retinal layers, with sparing the foveola (fig 1), which we found in 37% of children with severe malaria. However, there was no difference in the level of vision between patients who had macular whitening, including foveal involvement, and those who had not. This has implications for theories of pathogenesis of retinal signs in cerebral malaria.

It was not possible to measure visual acuity during the acute illness, because children were either in coma or prostrate. Patients were discharged soon after their coma and parasitaemia resolved, hence an accurate measure of visual acuity on discharge would not have been possible. The proportion of children attending for hospital follow up (68%) was high for this setting, and we were able to record acuity in 86%.

The methods used to measure visual acuity in young children differ according to the subject’s age, language development, and cooperation. Tests that involve preferential looking at graduated targets of interest, such as Cardiff cards, are used with preverbal children. Verbal children can identify pictures or symbols, or match optotypes or letters to ones presented at a distance. Sheridan-Gardiner single letters are commonly used for this, and once subjects know letters, they can read the single optotypes before graduating to a Snellen chart.

We encountered a number of difficulties in measuring vision in young children with tasks that were often outside their cultural norms. The measurement of visual acuity was done in a hospital environment during a follow up visit.
where capillary blood was routinely sampled, and this may have reduced cooperation.

Lea symbols, symbolic optotypes, which all blur to a circle, have been developed for children. It has been suggested they eliminate cultural biases and have been used successfully with native American children. We found verbal Malawian children were less good at identifying Lea symbols than matching letters. This may be because children in Malawi, particularly ones from rural areas, are not familiar with abstract pictures or symbols. They generally do not have access to picture books or drawing materials. They do have some exposure to letter shapes, but do not have systematic preschool teaching.

Cardiff preferential looking cards were used for children from 6 months, up to 5 years. Visual acuity in the verbal children was first attempted using Sheridan-Gardiner letters and a matching card, and if they were unable to match letters then Cardiff cards were used. The unfamiliarity with letters and lack of schooling may account for the necessity of using Cardiff cards in relatively older children. These children were also not sufficiently cooperative to perform acuity testing with the illiterate E chart.

Sheridan-Gardiner letters with a matching card were used for children aged 4–6 ½ years. Children from 6 up to 14 years were generally able to use the Snellen chart with or without a matching card. Refraction was not done, which may have reduced some visual acuities recorded, but this would have been a consistent effect across groups compared.

The necessity of using different methods of vision testing in different age groups introduces a potential age bias. However, there was not any difference in the age of children with and without macular whitening (Student’s t test, p = 0.70). We therefore do not believe that this has introduced systematic bias into our analysis.

During the course of this study there were six (4.2%) patients with cortical blindness after cerebral malaria, who did not fix and follow large objects on discharge. This incidence is consistent with those reported in studies of neurological sequelae after cerebral malaria in children (3.6–5.9%). These studies did not include an ophthalmologist's assessment, and results of dilated funduscopy were not reported.

One study of cortical blindness in a tertiary ophthalmic clinic in Nigeria found eight of 22 (36%) cases were caused by cerebral malaria. All cases had normal fundi, most (6/8) had other associated neurological deficits, and seven had some visual recovery within 6 weeks. All cases of cortical blindness reported here were accompanied by other neurological deficits, most commonly aphasia, deafness, ataxia, and hypotonia.

Four of the patients who were unable to fix and follow, had normal ocular fundi during admission. We infer that lack of visual behaviour acutely after cerebral malaria is not due to retinopathy, and that it is usually associated with other sensory or motor deficits. It indeed appears most likely to be a cortical phenomenon. Retinal changes including macular whitening, do not appear to contribute to apparent visual deficits following cerebral malaria.

Cortical blindness does not appear to be related simply to raised intracranial pressure indicated by papilloedema during the acute illness. The four patients in this group with papilloedema during admission all had good acuity on recovery.

Macular whitening does not closely resemble exudation, or extracellular oedema, and the results of this study support a different pathogenesis. Macular oedema centred on the fovea would be expected to affect children's visual acuity, and would normally take longer than a month to resolve.

On fluorescein angiography macular whitening is not accompanied by capillary non-perfusion or fluorescein leakage. We postulate that macular whitening is caused by cellular swelling of the inner retinal layers due to relative

| Table 1 Six patients with cortical blindness following cerebral malaria. All patients did not fix or follow at time of discharge |
| Age (months) | Retinal changes | Other deficits on discharge | Day of follow up | Vision at follow up |
| 23 | Normal | Aphasic, deaf, hypotonic, | 39 | No F & F |
| 36 | Normal | hemiparesis | 14 | 6/9 5 |
| 22 | Mild | Aphasic, deaf | 30 | F & F only |
| 26 | Normal | Ataxic, ataxic, hypotonic* | 7 | No F & F |
| 57 | Severe | Dicorticate, deaf | 14 | No F & F |
| 15 | Normal | Hemiparesis, aphasic, gaze palsy | 6 | F & F large objects |

F & F = fixing and following.
*Previous developmental delay and congenital cataracts and therefore excluded from analysis of outcomes.
hypoxia. Macular whitening is similar in appearance and angiographic findings to patchy ischaemic retinal whitening recently reported to be an uncommon early feature of central retinal vein occlusion with good visual recovery.14

In cerebral malaria intravascular sequestration of erythrocytes parasitised by P falciparum occurs in both the brain and the retina.15 The parasites metabolise oxygen and haemoglobin, which we believe causes a relative deoxygenation or hypoxia leading to intracellular oedema, and hence reversible opacification. Electoretinographic evidence suggests that ganglion cells are dysfunctional in macular whitening which would account for the typical sparing of the foveola.16 With resolution of the metabolic deficit intracellular oedema would reverse, allowing a normal visual acuity on recovery.

Other possible causes of intracellular swelling are toxic products produced by P falciparum, such as glycosylphosphatidylinositol (GPI)17,18 high concentrations of cytokines such as tumour necrosis factor α,19 or local factors such as nitric oxide, all of which have been shown to be important in the pathogenesis of cerebral malaria.20,21 However, macular whitening is centred on the most metabolically active part of the retina, without predilection for perivascular areas most exposed to these blood borne elements. We therefore believe that this makes a hypoxic explanation more likely. Whether this has relevance to cerebral pathogenesis remains speculative.

Further work with older children with cerebral malaria would show whether these peripheral vessel changes have hitherto undetected effects on the visual field.

We conclude that retinal changes in severe malaria do not appear to affect the visual acuity at 1 month. This makes excudation an unlikely cause, and supports the theory that macular whitening is due to reversible cellular swelling in response to a metabolic deficit.

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