Prognostic Significance and Course of Retinopathy in Children With Severe Malaria

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Objectives: To relate retinal findings in children treated for severe malaria to disease outcome and to determine the course of changes in the fundus.

Methods: A prospective study of children with cerebral malaria (CM) and severe malarial anemia admitted to the Malaria Research Project, Blantyre, Malawi, during 2 malaria seasons. Indirect and direct ophthalmoscopy were performed on admission and daily, subject to the patient's cooperation.

Results: Three hundred twenty-six patients (91%) with complicated malaria were recruited. Two hundred seventy-eight patients had CM and of these 170 (61%) had some degree of retinopathy; 25 (53%) of 47 with severe malarial anemia had retinopathy. In CM, retinopathy was associated with subsequent death (relative risk, 3.7; 95% confidence interval, 1.6-8.5) and papilledema conferred the highest risk (relative risk, 4.5; 95% confidence interval, 2.7-7.6). Increasing severity of retinal signs was related to increasing risk of a fatal outcome ($P<.05$), independent of papilledema. In survivors, retinal signs were associated with prolonged time to recover consciousness ($P<.001$). Patients with severe malarial anemia had better outcomes and less severe retinopathy than those with CM. In 116 patients with CM, fundi were followed up longitudinally during admission and in 27 patients after hospital discharge. A large increase in retinal hemorrhages was associated with death ($P=.02$). Retinal signs resolved over 1 to 4 weeks without retinal sequelae.

Conclusions: In childhood CM, severity of retinopathy is related to prolonged coma and death. Our results support the hypothesis that retinal signs in CM are related to cerebral pathophysiology.

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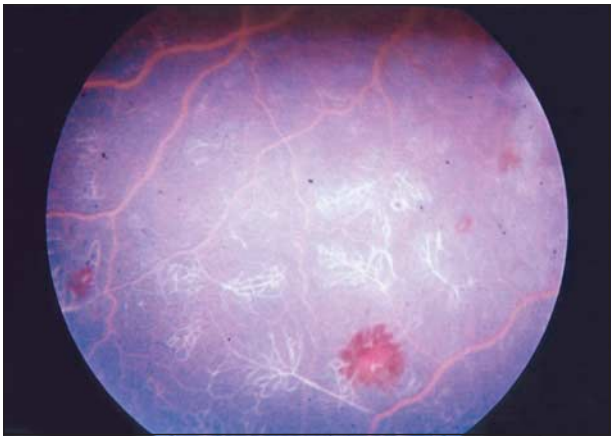
SEVERE FORMS OF MALARIA DUE to *Plasmodium falciparum* infection still have high mortality and morbidity in sub-Saharan Africa. *Plasmodium falciparum* malaria causes 1.5 to 2.7 million deaths every year,[1] preponderantly in African children who have cerebral malaria (CM) or severe malarial anemia (SMA). In children, CM is characterized by acute coma, associated with metabolic acidosis and anemia; while in SMA anemia and acidosis predominate. Complications seen in adults, such as renal failure, pulmonary edema, and disseminated intravascular coagulation are uncommon. Even with optimum hospital care, childhood CM has a mortality rate of 15%, and about 10% suffer neurological sequelae, such as epilepsy, ataxia, hemiplegia, and cortical blindness.[2,3]

Severe malaria is associated with a unique cluster of retinal signs that have been described in children in Malawi, Kenya, and Gambia.[4-6] These signs are best seen by indirect ophthalmoscopy and have been found in 77% of patients with CM.[4] The characteristic features include whitening of the macula with sparing of the foveola; whitening of the peripheral retina; retinal vessel discoloration to pale orange or white, including whitening of the capillary network (**Figure**); multiple retinal hemorrhages, which are preponderantly white centered; and papilledema.[6] The vessel whitening can be in the form of delineation of the central blood column.

Vessel whitening may be due to the presence of cytoadhered, or sequestered, erythrocytes in which hemoglobin has been metabolized by intracellular parasites. Sequestration of dehemoglobinized, parasitized erythrocytes has been shown on histopathologic examination to occur in retinal vessels of eyes with vessel whitening.[7] The number of retinal hemorrhages has been shown to correlate with cerebral hemorrhages at postmortem examination.[8] The pathophysiology of retinal whitening remains unclear, although intracellular swelling in response to hypoxia is suspected.[9]



White-centered hemorrhage and vascular changes in the form of vessel whitening in a child with cerebral malaria.

The relationship between retinal lesions and outcome in CM has not been fully explored. Lewallen et al[10] found papilledema and the presence of retinal edema (whitening) to be associated with death in Malawian children. Other studies have focused on retinal hemorrhages and papilledema observed by direct ophthalmoscopy.[11-14] Retinal hemorrhages, edema, and papilledema have been recorded in adults with CM.[13,15] To our knowledge, the course of retinal signs in CM has not been formally investigated.

We conducted a prospective study of all children admitted to an African central hospital and treated for CM or SMA during 2 consecutive malaria seasons. We aimed to relate the presence and severity of retinal signs to clinical outcome and to determine the course of the retinal signs.

METHODS

The study cohort was all children with CM or SMA admitted to the Malaria Research Project ward at the Queen Elizabeth Central Hospital, Blantyre, Malawi. They were studied prospectively during 2 malaria seasons, from January to June 1999 and 2000. Cerebral malaria was defined as an acute onset coma maintained for at least 4 hours after admission, scoring 2 or less on the Blantyre Coma Scale,[3] with *P falciparum* parasitemia. Other explanations for altered consciousness, such as hypoglycemia, postictal state, or meningitis were excluded. Severe malarial anemia was defined in patients with parasitemia, a hematocrit reading of 15% or less, and a Blantyre Coma Scale score of 3 or higher. The CM group included all patients with SMA who were unconscious (Blantyre Coma Scale score <3).

All children were treated according to a protocol with intravenous quinine and fluids by weight and also glucose, anticonvulsants, and antipyretics according to need. Intravenous antibiotics were given for concurrent infections, or if a lumbar puncture to exclude meningitis was not done. Screened blood transfusions were given for life-threatening anemia. All children followed the same treatment protocol with no differentiation between those with and without retinal signs.

Clinical observations, including the Blantyre Coma Scale score, were made every 2 hours until coma resolved. Coma resolution time (the time taken to recover to a Blantyre Coma Scale score of 5) was noted. Outcome on discharge was recorded as full recovery, recovery with neurological sequelae, or death. The Malawi College of Medicine Research and Ethics Committee gave ethical approval. Patients were recruited after their parents or guardians had given permission in their own language.

Recruited children underwent indirect and direct ophthalmoscopy by an ophthalmologist (N.A.B. and C.S. in 1999 and N.A.B in 2000) following pupil dilatation with a combination of 1.0% tropicamide hydrochloride and 2.5% phenylephrine hydrochloride. Findings were recorded on standardized charts with acceptable interobserver concordance.[16] Hemorrhages were graded using an ordinal frequency scale; macular whitening (MW) and foveal whitening (FW) by estimated area of involvement, peripheral whitening (PW) by an ordinal severity scale (range, 0, 1+, 2+, and 3+) for each quadrant and averaged to give a composite score, and vessel changes (VC) by number of quadrants involved.

Children underwent ophthalmoscopy on admission, or after their clinical condition had stabilized. During 1999, examinations were repeated daily subject to the patient's cooperation, or until the results of 2 consecutive examinations were normal. Ophthalmoscopy was attempted in children attending a follow-up appointment with particular attention paid to those with retinal signs during admission.

Data were analyzed using Stata (release 6, Stata Corp, College Station, Tex). Groups with and without retinopathy were compared to establish whether they were comparable for demographic features and treatment received. Associations were investigated between clinical variables on admission and the presence of retinopathy, using the Mann-Whitney and χ^2 tests. The relationship between severity of retinal signs and hematocrit reading was examined by Cuzick's nonparametric test for trend.[17] The relationship between severity of retinal signs and death was examined by χ^2 for trend and univariate logistic regression.

Multivariate logistic regression analysis was performed, with death as the dependent variable, and including all predictor variables that were related to death with a $P<.10$ in univariate analysis. This was done to establish whether retinal signs were independent of each other and other clinical features in predicting death. The other outcome measure was coma resolution time that was used as the dependent variable in a multivariate linear regression with retinal signs as predictor variables.

Changes in retinal signs over time were investigated for relationships with outcome. Change was defined according to the following preset criteria for identifying change in retinopathy over time: (1) a change in the severity grade of hemorrhages; (2) the development or resolution of papilledema; (3) a change in MW or FW by 2 severity grades based on size of area affected; (4) a change in PW by 1 grade in 2 or more quadrants, or by 2 or more grades in any quadrant; or (5) the appearance or resolution of VC in 2 or more quadrants. The eye with the most consistent view was used, or the right eye was used if both had a similar view.

RESULTS

The clinical course and outcome of CM and SMA were different; therefore, the results are given separately.

RETINAL FINDINGS IN CM

During the study period 304 patients were admitted with CM and 278 patients (91%) were recruited. Three children with prior neurological deficits were excluded from the study, and 23 were not recruited because of their death before ophthalmoscopy (9 patients), denial of consent (1 patient), or unavailability of observers (13 patients).

The median age of recruited patients was 2.8 years (age range, 4 months to 14 years) and 48.2% were males. The median time of ophthalmoscopy was 1 hour after admission (range, 0-48 hours); 73% were within 4 hours and 96% within 24 hours.

Forty-one patients (14.8%) died; 17 (6.1%) were discharged with neurological sequelae. All patients who were ultimately discharged with neurological sequelae were recruited. Neurological sequelae included ataxia, dysphasia, cortical blindness, deafness, hemiparesis, gaze palsy, and persistent coma.

The frequency of retinal changes in CM are given in **Table 1**. When patients with retinopathy were compared with those with normal fundi, there was no difference in age, sex, nutritional status, and medications given (**Table 2**). Patients with retinopathy were more likely to have respiratory distress ($P=.02$), had a higher average parasite density ($P=.02$), and were less likely to have repeated or prolonged convulsions (>5 recorded episodes during admission) than those without retinopathy ($P=.01$).

In addition, patients with retinal changes were more anemic (median hematocrit reading, 20%) than those without retinopathy (median hematocrit reading, 28%; $P<.001$) and were more likely to receive a blood transfusion. The severity of each individual retinal sign was negatively related to hematocrit reading ($P<.005$), except for papilledema ($P=.96$). There was no association between anemia and fatal outcome, patients who died were no more anemic than survivors (median hematocrit reading, 21% vs 24%; Mann-Whitney test, $P=.45$). The differences of other clinical parameters were not statistically significant.

Table 1. Frequency of Retinal Signs in Cerebral Malaria (CM) and Severe Malarial Anemia (SMA)

Retinal Sign	No. (%) of Patients	
	With CM	With SMA
Normal fundi	108 (39)	22 (47)
Any retinopathy	170 (61)	25 (53)
Hemorrhages	129 (46)	14 (30)
Peripheral whitening	123 (44)	21 (45)
Macular whitening	127 (46)	11 (23)
Vessel changes	90 (32)	10 (21)
Papilledema	41 (15)*	2 (4)

*Nine patients (3%) had papilledema alone.

Table 2. Characteristics of 278 Patients With Cerebral Malaria, Comparing Patients With Normal Fundi With Those With Retinal Changes*

Characteristics	Normal Fundi	Retinal Changes	*P* Value
Age, median, y	2.8	2.8	.89
Males	49	48	.82
Middle arm circumference, median, cm	15	15	.29
Weight, median, kg	10.8	11.0	.81
Anticonvulsants given	45	59	.21
Antipyretic given	73	68	.47
Antibiotic given	25	24	.88
Blood transfusion received	14	48	**<.001**
Blantyre Coma Scale score, mean	1 (1.3)	2 (1.4)	.066
Respiratory distress	23	37	**.02**
Temperature, median, °C	38.4	38.7	.079
Systolic blood pressure, median, mm Hg	110	104	.45
Admission blood glucose level, median, mg/dL	104	99	.31
Hypoglycemia during admission, median	18	15	.42
Hematocrit reading, %	28	20	**<.001**
Logarithm parasite density	4.6	5.0	.02
White blood cell count, median, $\times 10^3/\mu L$	9.7	9.6	.89
Repeated or prolonged convulsions	16	6	**.007**

SI units: To convert glucose values to millimoles per liter, multiply values by 0.05555.

*Medians are compared using the Mann-Whitney rank sum test and proportions using the χ^2_1 test. Data are given as percentages unless otherwise indicated. Statistically significant results are boldfaced.

RETINAL FINDINGS AND OUTCOME IN CM

The difference between the frequency of retinopathy in children who developed neurological sequelae (7/17; 41%) and those who fully recovered (128/220; 58%) was not statistically significant ($P=.17$). Survivors were analyzed as a group.

The presence and severity of retinal findings were analyzed in relation to fatal outcome (**Table 3**). Retinopathy was present in a significantly higher proportion of those who died compared with survivors ($P=.001$). The relative risk of death conferred by the presence of any abnormalities of the fundus was 3.7 (95% confidence interval, 1.6-8.5) and was also increased in the presence of papilledema, retinal hemorrhages, or vessel abnormalities.

The severity of retinal hemorrhages, VC, FW, and MW all showed significant, positive association with death by χ^2 for trend analysis (Table 3). The presence of moderate to severe grades of hemorrhages, VC, FW, and MW conferred a significantly increased relative risk of death.

Univariate logistic regression on the clinical and laboratory variables in Table 2 identified factors related to death with $P\leq.10$. These were retained for inclusion in a multivariate logistic regression of fatal outcome. The results of univariate logistic regression on the signs of the fundus are presented in **Table 4** and these were also included in the model. The clinical and laboratory variables consistently related to death in studies of CM in children are deep coma and hypoglycemia.[3,10,18-20] Respiratory distress or acidosis was also predictive of death in several studies of severe malaria.[21-23] Unfortunately, blood gas evaluation was unavailable because of equipment failure. However, respiratory distress, along with Blantyre Coma Scale score and blood glucose level on admission were included in the model. The full model is listed in **Table 5**. Papilledema and hemorrhages were independent predictors of death ($P\leq.01$) with greater odds ratios than any of the other factors. The other retinal signs were correlated with hemorrhages ($r>0.5$, $P<.001$).

In survivors coma resolution time was significantly longer in patients with retinopathy (median, 42 hours) than those with none (median, 29 hours; $P<.001$). Each sign was significantly related to the coma resolution time by univariate linear regression (**Table 6**) ($P<.005$). A minimal-effects regression analysis of fundus signs showed that hemorrhages, PW, and papilledema were independent in predicting prolonged coma (**Table 7**)($P<.05$).

All patients had blood cultures taken on admission, and in 9 patients (3%) with CM pathogens were cultured, mostly *Salmonella* species. Three patients with septicemia died; 1 had normal fundi and 2 had papilledema only.

Table 3. Presence and Severity of Retinopathy and Individual Retinal Signs Related to Outcome in 278 Children With Cerebral Malaria

Retinal Sign	n	No. (%) of Patients Who Died	*P* Value (χ^2 or χ^2 for Trend)*	Relative Risk of Death (95% Confidence Limits)	
				In Presence of Sign	Moderate to Severe Manifestation†
All patients	278	41 (15)	NA	NA	NA
Any retinopathy					
None	108	6 (6)	**.001**	3.7 (1.6, 8.5)	NA
Present	170	35 (21)			
Papilledema					
None	237	23 (10)	**<.001**	4.5 (2.7, 7.6)	NA
Present	41	18 (44)			
Hemorrhages					
None	149	15 (10)		2.0 (1.1, 3.6)	3.4 (2.0, 5.8)
1-5	85	10 (12)			
6-20	28	6 (21)	**<.001**		
21-50	12	7 (58)			
≥51	4	3 (75)			
Vessel changes					
None	188	19 (10)		2.4 (1.4, 4.3)	3.0 (1.7, 5.1)
≤1-2 Quadrants‡	40	6 (15)	**<.001**		
>1-2 Quadrants‡	50	16 (32)			
Foveal whitening					
None	183	20 (11)		2.0 (1.2, 3.5)	2.6 (1.4, 4.7)
<⅓ FA	64	11 (17)	**<.01**		
⅓ - ⅔ FA	22	8 (35)			
>⅔ FA	9	2 (22)			
Macular whitening					
None	151	18 (12)		1.5 (0.9, 2.7)	2.3 (1.3, 4.0)
<⅓ DA	62	6 (10)	**<.02**		
⅓ - 1 DA	43	11 (26)			
>1 DA	22	6 (27)			
Peripheral whitening					
None	155	18 (12)		1.6 (0.9, 2.8)	1.6 (0.9, 2.9)
0-0.90	44	7 (16)	<.17		
1-1.90	56	11 (20)			
2.00-3.00	23	5 (22)			

Abbreviations: DA, disc area; FA, foveal area; NA, not applicable.
*Statistically significant results are boldfaced.
†Moderate to severe disease (worse than the mildest positive category), that is, hemorrhages more than 5; macular whitening, one third or more of the DA; foveal whitening, one third or more of the FA; peripheral whitening, a composite score of 1.0 or more; vessel changes, 1 or more quadrants involved.
‡Quadrants indicate proportions of visualized quadrants involved.

Table 4. Results of Univariate Logistic Regression Analysis of Death by Papilledema and Individual Retinal Signs in Cerebral Malaria

Retinal Sign	Odds Ratio	SE	*P* Value*	95% Confidence Interval
Papilledema	7.28	2.79	**<.001**	3.4-15.4
Hemorrhages	2.09	0.35	**<.001**	1.5-2.9
Vessel changes	2.03	0.40	**<.001**	1.4-3.0
Foveal whitening	1.68	0.31	**.006**	1.2-2.4
Macular whitening	1.48	0.23	**.02**	1.1-2.0
Peripheral whitening	1.49	0.31	.06	1.0-2.3

*Statistically significant results are boldfaced.

RETINAL FINDINGS IN SMA

Forty-seven patients with SMA were recruited, 82% of admissions for SMA. Their median age was 2 years (age range, 5 months to 12 years). Their median hematocrit reading was 10%, and median hemoglobin concentration was 3.1 g/dL. There were 2 deaths (4%), in 1 of which the patient had had concurrent pneumonia.

Retinopathy was less common in SMA (53%) than in CM (61%) and tended to be less severe with fewer of the component changes (Table 1). In SMA all MW was in the mildest category, and only 1 patient had more than 5 hemorrhages. However PW and VC were almost as common as in CM. There were 5 patients admitted with critically severe anemia (hematocrit reading, 7%-8%) without malaria detectable by parasitemia; none had any retinal changes.

CHANGES IN RETINOPATHY DURING ADMISSION IN CM

The fundi of 116 children with CM were examined daily during a mean of 2.7 days. A single observer (N.A.B. or C.S.) performed all examinations on 103 (89%) of 116 children. Results of the initial examination showed no abnor-

Table 5. Multivariate Logistic Regression Model With Death as the Dependent Variable*

Variable	Odds Ratio	SE	*P* Value†	95% Confidence Interval
Papilledema‡	5.98	3.29	**.001**	2.0-17.6
Hemorrhages‡	2.11	0.60	**.008**	1.2-3.7
Blantype Coma Scale score	0.48	0.15	**.02**	0.3-0.9
White blood cell count	1.00	0.00	.05	1.0-1.0
Peripheral whitening‡	0.41	0.19	.06	0.2-1.0
Systolic blood pressure	0.98	0.01	.08	1.0-1.0
Vessel changes‡	1.42	0.48	.29	0.7-2.7
Respiratory distress	1.66	0.83	.31	0.6-4.4
Blood glucose level	0.95	0.07	.48	0.8-1.1
Foveal whitening‡	1.50	0.79	.45	0.5-4.2
Temperature	0.87	0.18	.50	0.6-1.3
Antipyretic given	1.30	0.69	.51	0.5-3.7
Antibiotic given	1.17	0.62	.78	0.4-3.3
Macular whitening‡	0.97	0.48	.95	0.4-2.6

*Variables included were related to death with $P<.10$ on univariate analysis.
†Statistically significant results are boldfaced.
‡Ocular fundus abnormalities.

mality in 44 children (38%), all of whom survived and only 2 (5%) of whom developed 1 to 5 hemorrhages.

Seventy-two children (62%) had retinal changes initially. The difference between the mortality in those whose retinopathy worsened (7/39 [18%]) and those whose retinopathy did not (2/33 [6%]) was not statistically significant ($P=.17$) (**Table 8**).

Patients with a large increase in the number of retinal hemorrhages (defined as progression by ≥2 grades, or to the most severe grade) were at an increased risk of death ($P=.02$) (Table 8). The relative risk of death in this group was 5.1 (95% confidence interval, 1.5-17.1). The intervals between these observations and subsequent death were three-quarter hour and, 2, 5, and 7 hours. There was no association between death and either the progression of other retinal signs or an increase in hemorrhages by 1 grade only.

RETINAL FINDINGS AFTER DISCHARGE

During the 1999 malaria season, 102 patients (60%) who had had CM attended for follow-up within 4 weeks of discharge. Twenty-seven children (26%) were sufficiently cooperative for fundus examination. Retinal signs had been present in 22 of these patients during admission; all were observed to be improving without any secondary retinal sequelae.

The progress of retinal signs after discharge is given in **Table 9**. Vessel changes persisted for up to 3 weeks. Macular whitening and FW resolved over 2 weeks. Peripheral whitening was not seen in any patient for longer than 7 days after discharge. This is longer than the acute clinical episode that generally resolves with therapy during 24 to 48 hours in those who recover fully.

COMMENT

This study has shown that retinal changes in CM are significantly associated with poor outcome. The time to regain consciousness is longer in patients with retinopathy, and the risk of death is increased 3.5-fold (95% confidence interval, 1.5-8.0). Coma recovery time and risk of death increase with increasing severity of retinal signs.

Table 6. Results of Univariate Linear Regression of Coma Resolution Time by Papilledema and Individual Retinal Signs in Cerebral Malaria

Retinal Sign	Regression Coefficient	SE	*P* Value*	95% Confidence Interval
Peripheral whitening	14.00	2.77	**<.001**	8.5-19.5
Foveal whitening	11.09	2.73	**<.001**	5.7-16.5
Hemorrhages	11.00	2.43	**<.001**	6.2-15.8
Macular whitening	9.42	2.06	**<.001**	5.4-13.5
Vessel changes	9.38	2.65	**<.001**	4.2-14.6
Papilledema	18.90	6.54	**.004**	6.0-31.8

*Statistically significant results are boldfaced.

Table 7. Results of Multivariate Linear Regression of Coma Resolution Time by Papilledema and Individual Retinal Signs in Cerebral Malaria Using Forward Stepwise Progression

Retinal Sign	Regression Coefficient	SE	*P* Value	95% Confidence Interval
Peripheral whitening	9.56	3.17	**.003**	3.3-15.8
Hemorrhages	6.14	2.75	**.03**	0.7-11.6
Papilledema	13.99	6.27	**.03**	1.6-26.3

*Statistically significant results are boldfaced.

The pathophysiology of CM is poorly understood, but these results, by relating severity of retinal signs to length of coma and to fatal outcome, support the hypothesis that retinal signs relate to cerebral pathophysiology. Papilledema and retinal hemorrhages were independent predictors of death. This suggests that papilledema and retinal changes are indicative of different pathophysiological processes that can occur together in CM but are independently related to poor outcome.

Our results support the findings of Lewallen et al[10]who studied 141 Malawian children with CM and found a relative risk of death with papilledema of 6.7, and with vascular abnormalities of 3.2, compared with our findings of 4.5 and 2.4, respectively. They found no association between death and the presence of retinal hemorrhages but had not evaluated the severity of retinal signs. Data from Lewallen et al were from patients enrolled in a therapeutic drug trial and more specific entry criteria may account for some variation in results. Other studies of retinal changes in CM are not directly comparable as they did not use indirect ophthalmoscopy[12,14] or were in adults.[11,13,15]

In patients with SMA, retinopathy was milder and disease outcomes were better. The number of deaths in this group were too small to analyze in relation to retinopathy.

We have found an important relationship between retinopathy and anemia in CM. There was a highly significant association between a low hematocrit reading and the severity of each retinal sign ($P<.005$), except pap-

Table 8. Progress of Retinopathy, and Specifically Hemorrhages, in 116 Patients With Cerebral Malaria Examined on 2 or More Occasions During Hospitalization Related to Outcome*

Initial Examination Finding	Progress	Those Who Died	Those Who Survived	*P* Value (Fisher Exact Test)†
Any retinopathy	Unchanged or improved	2 (6)	31 (93)	
	Worsened	7 (18)	32 (82)	.17
Hemorrhages	Changed ≤1 grade	4 (8)	47 (92)	
	Increased ≥2 grades	4 (40)	6 (60)	**.02**
	Unchanged or reduced	3 (8)	36 (92)	
	Increased	5 (20)	20 (80)	.25

*Data are given as the number (percentage) of patients.
†Statistically significant results are boldfaced.

Table 9. Progress of Retinal Signs after Discharge in 22 Patients With Retinal Signs During Admission*

		Week After Discharge			
	Total†	1	2	3	4
Vessel changes	10	2/2	0/1	2/3	0/4
Macular and foveal whitening	16	3/4	1/5	0/5	0/5
Peripheral whitening	15	2/5	0/5	0/5	0/4
Hemorrhages	19	3/3	1/5	2/3	5/10

*The numerator indicates the number of patients with the retinal sign still present, the denominator, the number of patients examined within each week.
†Total indicates the number of patients with a retinal sign during admission.

illedema. The relationship with anemia was independent of death, and anemia alone without parasitemia is insufficient to cause these retinal changes. None of 13 children with meningitis and severe anemia (hematocrit reading, <20%) examined during the study period had these specific retinal signs.

An association between retinal hemorrhages and anemia in complicated malaria has been previously noted,[4] but our findings show anemia to be related to the other retinal signs. The pathogenesis of acute anemia is complex, but its severity is related to the maximum parasitaemia.[24] Severe anemia is likely to be associated with high concentrations of sequestered, parasitized erythrocytes within the microvasculature, thought to cause retinal VC.[8] Similarly, high densities of rapidly metabolizing parasites in the retinal vasculature may produce relative hypoxia leading to intracellular edema. This has been proposed as a mechanism causing retinal whitening.[4]

To our knowledge, retinal changes in CM have not previously been followed up systematically over time. We found that a large increase in the number of retinal hemorrhages after admission was associated with death. This finding is based on only 4 deaths in each group and so this needs to be treated with caution. However, its clinical significance can be illustrated by the fact that the interval between the observation of a substantial increase in hemorrhages and subsequent death was short (three quarters of an hour and 2, 5, and 7 hours). This premorbid development of many retinal hemorrhages is a new observation and may indicate the development of coagulopathy with fibrin deposition as part of the terminal process in these children. Fibrin deposition in cerebral capillaries has been noted in autopsy studies,[25-27] including studies in this research programme (Richard Carr, MRCPath, written communication, March 12, 2001).

The remaining analysis of our longitudinal data failed to show statistically significant associations between deterioration in retinal signs, either individually or collectively, and fatal outcome of the disease. The changes in retinal signs were limited after admission, and our analysis was restricted by the few deaths in this group. Deaths tend to occur soon after admission to the hospital, precluding serial examinations of the fundus.

Retinal changes in CM took longer to resolve than the clinical episode. Vascular changes were persistent for up to 3 weeks. This has an important bearing on theories regarding the mechanism of coma and death in CM.[28] Retinal vascular changes are associated with parasitized erythrocytes sequestered in retinal vessels.[8] Retinal vascular changes and sequestered erythrocytes (which may contain dead parasites) are still present long after the child has regained consciousness. Assuming retinal vascular changes occur in parallel with cerebral sequestration, this finding of prolonged retinal vessel whitening suggests that the physical presence of parasitized erythrocytes alone is insufficient to maintain coma.

There were no secondary retinal changes or ischemic sequelae in the 4 weeks after discharge. This supports the findings of Hero et al[4] that showed no evidence of microvascular occlusion or leakage on fluorescein angiography.

Parasitemia is common in the population served by the Queen Elizabeth Central Hospital, and so incidental parasitemia can occur in any comatose patient. Three children having a clinical diagnosis of CM died with a septicemia, while none had retinal changes other than papilledema. In the context of this study, this weakens the power of retinal signs to predict death. In the wider context, patients with apparently fatal CM and no malarial retinopathy may, in fact, have other factors contributing to coma and death. We emphasize the need to look for these factors in patients without retinopathy who do not have rapid recovery from coma. Conversely, retinal changes, by nature of their specificity, are valuable in confirming a diagnosis of CM in a comatose child with parasitemia. Cerebral malaria is a clinical diagnosis complicated by the presence of incidental parasitemia in this population, and ophthalmoscopy provides valuable diagnostic information.

This study demonstrates the value of ocular examination by indirect and direct ophthalmoscopy in patients with CM. We have shown that the presence and severity of retinal signs are significant predictors of prolonged coma and death. The previously reported link between retinopathy and outcome in CM has been strengthened and clarified by these findings. The presence of retinopathy, albeit in a milder form, is reported in SMA. It will be important to assess the extent to which nonspecialized practitioners in malarial areas can identify some or all of the changes described.

Our findings are consistent with the hypothesis that retinal changes in CM relate to cerebral pathophysiological processes. Retinal features are an integral part of the clinical picture, and ophthalmic observations can contribute to continuing studies of pathophysiological processes and therapeutic interventions.

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