

OCULAR LESIONS ASSOCIATED WITH MALARIA IN CHILDREN IN MALI

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Abstract. This study sought to estimate the frequency of ocular complications in malaria and its prognostic value in Mali. A total of 140 children (aged 6 months to 9 years) with severe malaria (105 with cerebral malaria, 35 without neurological complications) were compared with 34 children with mild malaria and 82 children with nonmalarial fever. Ocular lesions were rare in the mild malaria group (5.8%). Retinal hemorrhages occurred in 11.8% of the children in the severe noncerebral malaria group. Cerebral malaria was associated with retinal hemorrhages (22.9%) and retinal edema (10.5%). No association was found between ocular signs such as retinal hemorrhages or retinal edema and mortality. Exudates, papilledema, and the presence of cottonwool spots were associated with an increased risk of death. Coma score and convulsions were significantly associated with death but not with ocular signs. The presence of retinal signs in a child in a malaria-endemic area may signal a case of severe malaria.

Ocular complications occur frequently in cases of severe malaria.¹ Some lesions, such as extramacular or papilledema, have been related to a fatal outcome in cerebral malaria.² In this study, our aim was to estimate the frequency of ophthalmic lesions and their prognostic value among children with severe malaria in West Africa where to our knowledge, no such study has been conducted. The study was carried out in a hospital setting of Bamako, Mali, from October 1996 to January 1997, the peak of the malaria transmission season. Children aged 6 months to 9 years with severe malaria, with or without cerebral complications, were compared with 2 control groups, one with uncomplicated *P. falciparum* malaria and the other with nonmalarial fever.

Coma was graded according to the Molyneux coma scale³ derived from the Glasgow coma scale,⁴ with a decreasing score of 5 to 0 according to the graveness of symptoms. Abnormal ocular fundus was documented by retinography. Thick blood smear was used to quantitate parasitemia, the ParaSight-F test performed, and a manual test for qualitative detection of histidine rich protein-2 (HRP-2) of *Plasmodium falciparum* directly on total blood were performed. Venous blood samples were drawn to test for serum glucose and hemoglobin levels and for hemoglobin electrophoresis.

Cerebral malaria was defined as $> 1,000$ trophozoites/mm³, an axillary temperature $\geq 37.5^\circ\text{C}$, and one or more of the following complications: coma with a Molyneux score ≤ 3 , > 2 convulsions, or an obtundation (Molyneux score = 4). Children with a negative blood smear test but a positive ParaSight-F test, in the absence of any other identified cause of fever—and if they improved after receiving antimalarial treatment—were also considered to have cerebral malaria. Severe noncerebral malaria was defined as parasitemia $\geq 1,000$ trophozoites/mm³, associated either with severe anemia (hemoglobin ≤ 5 g/100 mL), hypoglycemia (≤ 0.40 g/L or ≤ 2.26 mmol/L), temperature $\geq 40^\circ\text{C}$, or parasitemia $\geq 100,000$ trophozoites/mm³.

The nonsevere malaria control group included children with temperature $\geq 37.5^\circ\text{C}$, 1,000 to 80,000 trophozoites/mm³, and no signs to suggest severe malaria. The fever control group included children with a temperature of $\geq 37.5^\circ\text{C}$ without evidence of blood parasites and with a negative ParaSight-F test.

One hundred forty children with severe malaria were in-

cluded in the study, 105 with cerebral malaria and 35 without neurological complications. Concurrently, 34 children with simple malaria and 82 children with fever but without malaria were included as controls.

In the fever control group, no ocular signs were observed, and in the nonsevere malaria group, 2 children (5.8%) experienced retinal hemorrhage or retinal edema. In patients with severe noncerebral malaria, retinal hemorrhage was the only sign encountered (11.8%). Retinal hemorrhages and retinal edema were the most frequent manifestations in cerebral malaria (22.9% and 10.5%, respectively), followed by vascular sinusitis, papilledema, and exudates. All signs were less frequent than in a Malawian cohort reported by Lewallen and others.² Similar to the study of Looreesuwan and others,⁵ papilledema appeared rare in our patients with cerebral malaria.

Frequency of ocular signs increased with delay for consulting and with the length of the coma. Retinal hemorrhages were more frequent among children older than 2, with > 2 convulsions a day, or with a temperature $\geq 40^\circ\text{C}$ (Table 1). Children with severe anemia were also more likely to experience retinal hemorrhages (40% versus 19.3%, $P = 0.07$) or retinal edema (20.0% versus 9.1%, $P = 0.20$). Unlike observations in Malawi,² hemorrhages were less frequent in patients with hypoglycemia (7.1% versus 25.3%, $P = 0.13$) and in patients in deep coma (18.3% versus 32.3%, $P = 0.11$). Frequent retinal hemorrhages have been described in people with hemoglobinopathies,⁶ but we did not observe ocular signs in the 7 children with abnormal hemoglobin levels ($P = 0.19$). This could be explained by the presumed protection of heterozygotic forms against severe forms of malaria or by less favorable conditions for the parasite. As Lewallen and others,² we did not find any evidence of correlation between parasitemia and ocular signs.

The mortality rate was 26.7% in the cerebral malaria group (46.7% in the presence of anemia and 21.6% in the absence of anemia) and 5.7% in severe malaria without neurological signs (16.7% if severe anemia and 3.4% if not). No child in the control groups died. Mortality increased with delay in seeking care, which highlights the importance of early diagnosis and treatment. Mortality decreased with age (Table 2). Depth of coma was a significant risk factor for death, as were the number of convulsions (54.5% if > 5 in the first 24 hours). Tem-

TABLE 1

Variables associated with ocular signs in children with cerebral malaria

Variable	Affected, n (%)	Hemorrhage, n (%)	P value	Edema, n (%)	P value
Age					
≤ 2 years	21 (20.0)	3 (14.3)		2 (9.5)	
> 2 years	84 (80.0)	21 (25.1)	0.23	9 (10.7)	0.62
Convulsions per day					
< 2	70 (66.7)	13 (18.6)		7 (10.0)	
2-5	24 (22.9)	9 (37.5)		2 (8.3)	
> 5	11 (10.5)	2 (18.2)	0.15	2 (18.2)	0.66
Scoring of coma					
≤ 2	71 (67.6)	13 (18.3)		8 (11.3)	
> 2	34 (32.4)	11 (32.3)	0.11	3 (8.8)	1
Temperature at Day 1					
< 40	93 (88.8)	20 (21.5)		9 (9.7)	
≥ 40	12 (11.2)	4 (33.3)	0.46	1 (8.1)	1
Serum glucose (g/L)					
≤ 0.40	14 (13.3)	1 (7.1)		1 (7.1)	
> 0.40	91 (86.7)	23 (25.3)	0.13	10 (11.0)	1
Hb* (g/L)					
≤ 5	15 (14.6)	6 (40.0)		3 (20.0)	
> 5	88 (85.4)	17 (19.3)	0.07	8 (9.1)	0.20
Electrophoresis of Hb					
Abnormal	7 (6.7)	0 (0.0)		0 (0.0)	
Normal	98 (93.3)	24 (24.5)	0.19	11 (11.2)	1
Parasitemia (/mm ³)					
< 1,000	10 (9.6)	2 (20.0)		0 (0)	
1,001-50,000	34 (32.7)	10 (29.4)		3 (8.8)	
> 50,000	60 (57.7)	12 (20.0)	0.56	8 (13.3)	0.41

* HB = hemoglobin.

TABLE 2

Prognostic factors analysis for children with cerebral malaria

Variable	Affected, n (%)	Mortality, n (%)	Relative risk	P value
Age				
≤ 2 years	21 (20.0)	8 (38.1)	1.60	0.19
> 2 years	84 (80.0)	20 (23.8)	1	
Convulsions per day				
< 2	70 (66.7)	16 (22.9)	1	
2-5	24 (22.9)	6 (25)	1.09	0.83
> 5	11 (10.5)	6 (54.5)	2.39	0.002
Scoring of coma				
≤ 2	71 (67.6)	25 (35.2)	4.34	0.004
> 2	34 (32.4)	3 (8.8)	1	
Temperature at Day 1 (°C)				
< 40	93 (88.8)	24 (25.8)	1	
≥ 40	12 (11.2)	4 (33.3)	1.29	0.73
Serum glucose (g/L)				
≤ 0.40	14 (13.3)	9 (64.3)	3.08	0.002
> 0.40	91 (86.7)	19 (20.9)	1	
Hb* (g/L)				
≤ 5	15 (14.6)	7 (46.7)	2.16	
> 5	88 (85.4)	19 (21.6)	1	0.05
Electrophoresis of Hb				
Abnormal	7 (6.7)	3 (42.9)	1.68	0.38
Normal	98 (93.3)	25 (25.5)	1	
Parasitemia				
< 1,000	10 (9.6)	3 (30.0)	1	
1,001-50,000	34 (32.7)	10 (29.4)	0.98	1
> 50,000	60 (57.7)	15 (25.0)	0.83	0.7
Ocular lesions				
Retinal hemorrhages	24 (22.9)	6 (25.0)	0.92	0.83
Retinal edema	11 (10.5)	3 (27.3)	1.03	0.75
Perimacular edema	9 (8.6)	1 (11.1)	0.82	0.94
Exudates	1 (1.0)	1 (100)	3.85	0.26
Cottonwool spots	3 (2.9)	2 (66.6)	2.62	0.17
Papilla edema	1 (3.0)	1 (100)	3.85	0.26

* Hb = hemoglobin.

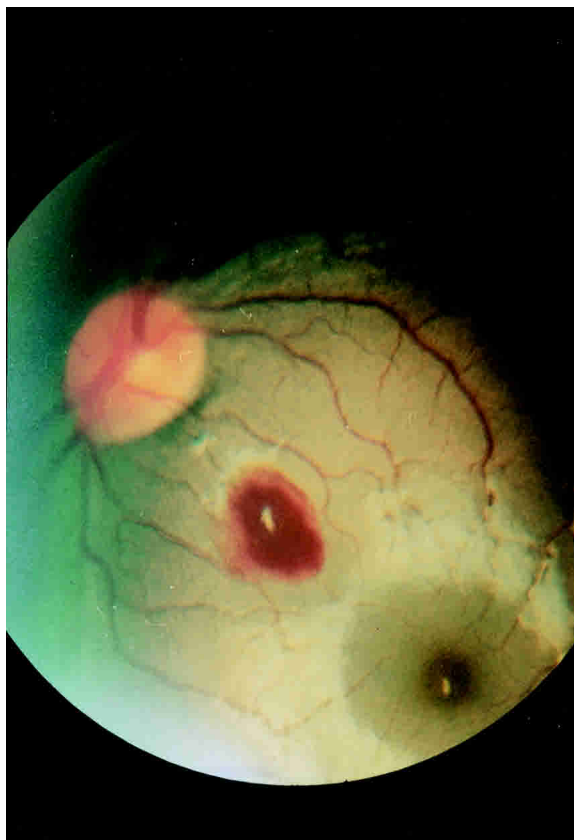


FIGURE 1. A new single hemorrhage between papilla and macula.



FIGURE 2. Resorption of a hemorrhage with white level.

perature was not significantly linked with mortality. Hypoglycemia and anemia were significantly associated with high mortality in cerebral malaria ($P = 0.002$ and 0.05 , respectively). Parasitemia did not influence death rates significantly; of interest, hemoglobinopathies were associated with an increased death rate.

Retinal hemorrhage was not predictive of fatal outcome in cerebral malaria. We could not find evidence of a relationship between retinal edema and mortality. However, Lewallen and others⁷ reported a higher risk of death, although they used a more restrictive case definition of cerebral malaria (Molyneux score ≤ 2) than we did. As Lewallen and others,⁷ we believe that papilledema is predictive of death. Nevertheless, even if vascular sinuosity, blurring of the optic disk, or cottonwool spots had been observed in children who later died, the small number of children who experienced such events did not allow us to infer the existence of a significant link.

Ocular signs observed in complicated malaria are linked to signs classifying the severity of the disease. In cases of severe malaria, particularly if a platelet count is not available, ophthalmic examination should be performed, and patients who develop ocular signs or symptoms should be carefully assessed and observed.

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REFERENCES

1. Gross J, Gross FJ, Friedman AH, 1991. Systemic infections and inflammatory diseases. Tasman W, Jaeger EA, eds. *Duane's Clinical Ophthalmology*. Vol. 5. Revised edition. Philadelphia: JB Lippincott, 33: 1-45.
2. Lewallen S, Bakker H, Taylor T, Wills B, Courtright P, Molyneux ME, 1996. Retinal findings predictive of outcome in malaria. *Trans R Soc Trop Med Hyg* 90: 144-146.
3. WHO, 1990. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 84 (Suppl 2): 1-22.
4. Teasdale G, Jennett B, 1974. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 2: 7872.
5. Looreesuwan S, Warrel D, White NJ, 1983. Retinal hemorrhage, a common physical sign of prognostic significance in cerebral malaria. *Am J Trop Med Hyg* 32: 911-915.
6. Pichard E, Serre L, Coulibaly D, 1991. Causes générales des hémorragies rétinienes et vitréennes au Mali. *Bull Soc Pathol Exot* 84: 1021-1027.
7. Lewallen S, Taylor TE, Molyneux ME, Wills BA, Courtright P, 1993. Ocular fundus findings in Malawian children with cerebral malaria. *Ophthalmology* 100: 857-861.