

Ophthalmoscopic abnormalities in adults with falciparum malaria

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Summary

We studied 424 adults with falciparum malaria admitted over 28 months. They were divided into three groups: cerebral malaria ($n=214$); severe non-cerebral malaria ($n=58$); and uncomplicated malaria ($n=152$). Fundus examination was done daily from admission to discharge, and weekly thereafter in those with persistent changes. All patients were treated by a protocol based on WHO guidelines. Ophthalmoscopic abnormalities were: retinal haemorrhages, 40 (9.43%) (25 cerebral malaria, 10 severe non-cerebral and five uncomplicated malaria); papilloedema, 17 (7.94%) cerebral malaria and two uncomplicated malaria; blurring of disc margins, 25 (11.68%) cerebral and seven non-cerebral; retinal

oedema, six (2.80%) cerebral and five non-cerebral malaria; disc pallor, five patients all with cerebral malaria; vitreous haemorrhage and hard exudate in one patient each, both cerebral malaria. Retinal haemorrhage was associated with cerebral malaria and severe non-cerebral malaria, especially with severe anaemia ($p<0.001$), as compared to uncomplicated malaria ($p<0.01$). The association of papilloedema and cerebral malaria was highly significant compared to severe non-cerebral malaria ($p<0.001$). None of these findings was associated with statistically significant mortality, except disc pallor in cerebral malaria ($p<0.05$).

Introduction

Malaria is a common and potentially fatal parasitic infection in tropical areas.¹ *P. falciparum* malaria is usually associated with progression to severe and complicated diseases, with high incidences of morbidity and mortality in the tropics.

Bikaner district is part of western Rajasthan (India), situated along the India-Pakistan border. It is a desert zone with annual rainfall of 26.3 cm and a temperature range from 0 °C to 49 °C. In recent years, an increased annual rainfall caused by the El Nino Southern Oscillation^{2,3} has produced favourable condition for mosquito breeding, and repeated outbreaks of malaria.

Eye abnormalities have been described in malaria patients since 1879⁴ by various workers in different countries, including keratitis, uveitis, retinitis pigmentosa, optic neuritis and ocular muscle pareses.^{5,6} Some workers have found these changes to be of

great prognostic significance,^{7,8} others as indicators of severity,^{9,10} others still have found them to be of no specific significance.¹¹ Some workers have proposed retinal oedema and papilloedema to be important,^{7,8} while others have emphasized retinal haemorrhage.^{9,10} No such study has been made in this region. We examined these complications in patients of different categories of falciparum malaria, and their relative prognostic significance. We compare our results with those of other workers.

Methods

Patients and laboratory procedures

We studied 424 falciparum malaria patients of both sexes aged >14 years, admitted from August 1994 to December 1996 in the medical wards of PBM

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Hospital Bikaner. Patients were managed in separate wards, with a patient to nursing staff ratio of 4.5 : 1. All medicines were provided by the hospital administration. Treatment facilities included administration of drugs through infusion pumps, facilities for diagnosis and management of cardiac arrhythmias, and haemodialysis.

After thin and thick peripheral blood smear examinations, only those patients having positive asexual forms of *Plasmodium falciparum* were included. Each had a thorough clinical and biochemical examination, which included complete urine examination, blood glucose level (at the time of admission), blood urea, serum creatinine, serum bilirubin, complete blood count (TLC and DLC), haemoglobin, widal test, serum electrolytes, ECG, CSF, HBsAg in patients with jaundice, X-ray of the chest in patients with respiratory problems, and blood culture in those with signs of septicaemia. BT, CT, prothrombin time and platelet counts were measured in those with bleeding problems, CT scan was used in selected patients. Upper gastro-intestinal endoscopy was done in patients with haematemesis.

Other causes of fever and altered consciousness, such as hypoglycaemic coma, hepatic coma, meningitis, encephalitis, and enteric toxemia were ruled out by history and relevant investigations. Patients having diabetes mellitus, an intracranial space-occupying lesion (ICSOL), hypertension, history of epilepsy, alcoholism, head injury or chronic renal failure (CRF), all of which can alter intracranial tension and fundus findings, were not included in the study.

Fundus examination was done in all patients, after putting phenylephrine HCl 5% eye drops in both eyes, by direct ophthalmoscopy and indirect ophthalmoscopy, if required, at the time of admission, daily thereafter and at the time of discharge.

Treatment and follow-up

All patients were given i.v. quinine dihydrochloride 7 mg/kg loading dose over 30 min immediately, followed by 10 mg/kg over 4 hours, at 8 h intervals. The loading dose was not given to those who were already taking chloroquine/quinine in the peripheral hospital. Patients who became able to take oral medicine were given 600 mg three times a day, based on 1990 WHO guidelines.¹² Associated syndromes were managed according to WHO guidelines.¹³ Patients with persistent ophthalmoscopic changes at the time of discharge were followed-up weekly until the changes resolved completely.

Statistical analysis

The results for cerebral malaria were compared with those for non-cerebral malaria. Each fundus abnor-

mality was tested for association with outcome. Retinal haemorrhages and papilloedema were tested for prognostic significance. Statistical analysis was done using the χ^2 test.

Results

There were 424 malaria patients: 214 with cerebral malaria,¹² 58 with severe non-cerebral malaria¹² and 152 with uncomplicated malaria.¹² Details are shown in Table 1.

Discussion

A comparison of our results with those of other studies in the literature is shown in Table 2.

Retinal haemorrhage

Retinal haemorrhages were present in 40/424 (9.43%) patients of adult falciparum malaria, including 25 (11.68%) patients with cerebral malaria, of whom three had associated papilloedema, and two had blurred disc margins. Five (20%) of these 25 died, a mortality similar to the overall mortality in cerebral malaria (21.49%) in this region. Five patients of uncomplicated malaria also had retinal haemorrhages and all recovered completely. Ten patients with severe non-cerebral malaria had retinal haemorrhages and one also had associated retinal oedema. Eight patients of these had associated severe anaemia (Hb < 5 g%). All these patients recovered completely, whereas overall mortality in the patients with severe non-cerebral malaria was 5.17%. This suggests that retinal haemorrhage does not predict mortality in falciparum malaria patients. Retinal haemorrhages were single in 14 patients and multiple in 26, unilateral in 16 and bilateral in 24 patients. They were of varying sizes, and shapes, e.g. flame shaped, Roth's spot type, dot and blot, and boat-shaped. Haemorrhage was superficial in 24 and deep in 14 patients; in the remaining two patients it was both superficial and deep.

Regarding the incidence of ophthalmoscopic abnormalities, our findings are different from that of Poncet (1879),⁴ who observed these abnormalities in 10% of the total malaria patients; in our study, overall ophthalmoscopic abnormalities were present in 24.76% patients and retinal haemorrhages were present in 9.43% patients. His observation that 'presence of retinal haemorrhages always suggest pernicious malaria' was probably an exaggeration, because in our study it was present in 11.68% patients of cerebral malaria and 17.24% patients of severe non-cerebral malaria and in 3.28% of patients with uncomplicated malaria as well. Our findings

Table 1 Ophthalmoscopic findings in patients with plasmodium falciparum malaria

Patient	Findings	Cerebral malaria (<i>n</i> = 214) ¹		Severe non-cerebral malaria (<i>n</i> = 58) ²		Uncomplicated malaria (<i>n</i> = 152)	
		Patients (%)	Deaths (%)	Patients (%)	Deaths (%)	Patients (%)	Deaths (%)
1	Retinal haemorrhages	20(9.34) + 5*	5(25.00)	9 + 1*** (15.51)	0	5(3.26)	0
2	Papilloedema	14(6.54) + 3**	3(21.42)	0	0	2(1.30)	0
3	Retinal oedema	4(1.86)	1(25.00)	0	0	0	0
4	Disc pallor	4(1.86)	4(100.00)	0	0	5(3.26)	0
5	Blurred margins of disc	16(7.47)	3(18.75)	0	0	1(0.65)	0
6	Vitreous haemorrhage	1(0.46)	1(100.00)	0	0	0	0
7	Blurred margins of disc plus disc pallor	1(0.46)	0	0	0	0	0
8	Blurred margins of disc plus retinal oedema	1(0.46)	0	1(1.72)	0	0	0
9	Retinal haemorrhages* plus papilloedema**	3(1.40)	0	0	0	0	0
10	Retinal haemorrhages* plus blurred margins of disc	2(0.93)	0	0	0	0	0
11	Hyperaemia plus blurred margins of disc	5(2.33)	0	1(1.72)	0	4(2.63)	0
12	Hyperaemia of disc plus retinal oedema	1(0.46)	0	1(1.72)	0	0	0
13	Hard exudate	1(0.46)	0	0	0	0	0
14	Retinal haemorrhages*** plus retinal oedema	0	0	1(1.72)	0	0	0
15	Disc pallor plus retinal oedema	0	0	1(1.72)	0	1(0.65)	0
	Any finding in total	73(34.11)	17(23.28)	14(24.13)	0	18(11.84)	0
	Normal fundus	141(65.88)	29(20.56)	44(75.86)	3(6.81)	134(87.14)	0
	Total patients	214	46(21.49)	58	3(5.17)	152	0

* Includes three patients with associated papilloedema and two patients with blurring of disc margins. ** Includes three patients who also had associated retinal haemorrhage.

*** Includes one patient who also had associated retinal oedema.

¹ The findings associated with mortality in patients with cerebral malaria were retinal haemorrhage, papilloedema, blurred margins of disc, retinal oedema and disc pallor. One patient had vitreous haemorrhage and died. All four patients with disc pallor died. Hard exudates were present in one patient. Retinal haemorrhage associated with papilloedema was present in three patients with no mortality. Retinal haemorrhage, papilloedema, retinal oedema and blurring of disc margins were statistically insignificant ($p > 0.05$ each) but disc pallor was significantly ($p < 0.05$) associated with fatal outcome, while presence of any ophthalmoscopic finding as a whole was significantly associated with mortality ($p < 0.05$).

² Ten patients had retinal haemorrhages, of whom one also had neurological manifestations, and recovered completely, while none of the patients had papilloedema. Other retinal findings were also not associated with mortality. On the other hand, three (6.81%) of 44 with normal fundi died.

Table 2 Comparison with selected other studies

Reference Country Patients	9	14		18	10	7		19	8	This study	
	Thailand Adult	PNG Adult		Malawi <10 years	Zambia Child	Malawi Child		PNG Child	Malawi Child	India Adult	
	C	C	NC	C	C	C	NC	C	C	C	NC
<i>n</i>	144	24	26	131	67	56	50	71	141	214	210
<i>Findings</i>											
Retinal haemorrhage	21	6	8	8	11	20	1	20	52	20+5*	14+1**
Papilloedema	1					7		1	16	14+3*	2
Extramacular oedema						10			36		
Macular oedema						19			48		
Retinal oedema										4	
Blurred disc margins										16	1
Vessel narrowing or obstruction						11			31		
Papilloedema and/or extramacular oedema						15					
Disc pallor										4	5+2**
Vitreous haemorrhage										1	
Exudate	2 (soft)								9 (cws)	1 (hard)	
2 + findings										13*	10*
<i>Mortality</i>											
Total	30	1	0	20	11	7		15	13	46	3
Retinal haemorrhage	7	0	0	3	3	5#		14	1	5	0
Papilloedema		0	0			5#		1		3	0
Extramacular oedema						6#			12		
Macular oedema						7#					
Retinal oedema										1	
Blurred disc margins								5#		3	
Vessel narrowing or obstruction								10#			

without retinopathy. Retinal haemorrhages have also been described in severe anaemia from causes other than falciparum malaria by Rubstein *et al.*²² and Holt and Smith.²³ Our findings are similar to those of Davis *et al.*,¹⁴ who also observed a strong correlation between the presence of severe anaemia and retinopathy. There was no correlation of retinopathy with other laboratory data in this study. Of 10 patients with falciparum malaria and severe anaemia (Hb <5 g%), all had retinopathy and complete recovery similar to that observed by Davis *et al.*¹⁴ We did not observe any correlation between severity of illness or retinopathy, and the ultimate outcome of patients. Molyneux *et al.*¹⁸ observed retinal haemorrhages in eight (6%) of the 131 Malawian children studied. Three children died and one developed neurological sequelae. As the number of children with retinal haemorrhages in his study was small, they were unable to define its prognostic significance. According to the WHO report (1990),¹² retinal haemorrhages occur in about 15% of cases of cerebral malaria, which is similar to our study.

Our findings regarding retinal haemorrhages are also similar to those of Haslett,¹⁰ where retinal haemorrhages were present in 11 (16%) cases of cerebral malaria in a study on 67 Zambian children. These were all of Roth's spot type with pale centre, and in six (54.54%) cases, they were multiple. There was no significant difference in mortality and haemoglobin concentration between the groups with and without retinal haemorrhages, but there was a trend towards increased mortality and lower haemoglobin in those patients with evidence of retinal haemorrhages. Haslett stressed importance of the geographical location regarding the presence of retinal haemorrhages i.e. 15% in Thailand,⁹ 31% in Zaire,¹¹ 28% in Papua New Guinea,¹⁴ and this may be the reason for the figure of 12% in our study. He further stressed that retinal haemorrhages should not be taken in isolation and

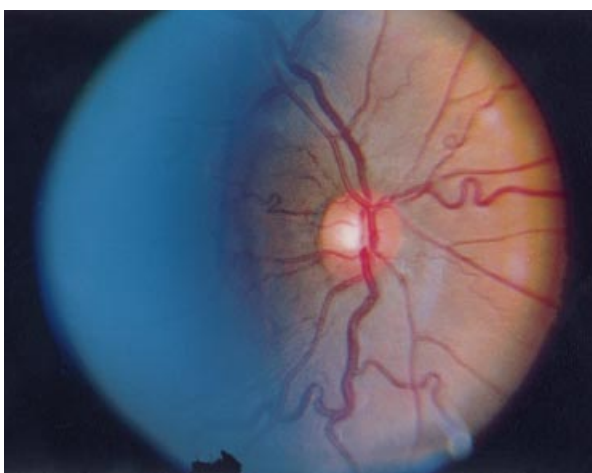


Figure 1. Marked venous dilatation and tortuosity in a case of cerebral malaria.

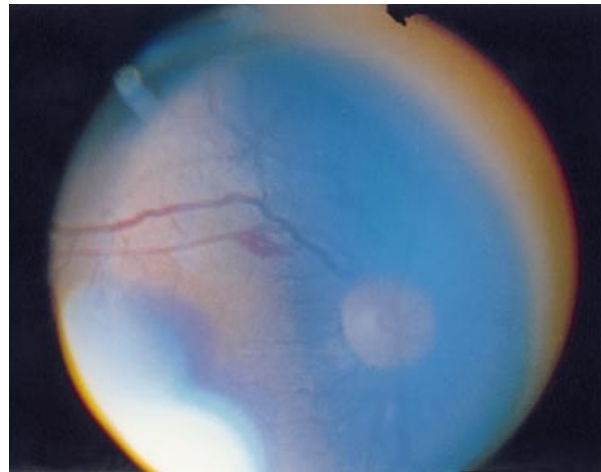


Figure 2. Superficial splinter-shaped haemorrhage along the superficial vessel in temporal quadrant in a case of falciparum malaria with severe anaemia.

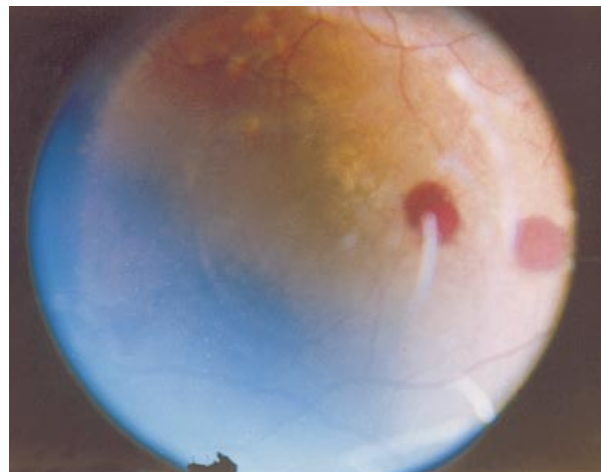


Figure 3. Two well-defined deep retinal haemorrhages about 1 mm in diameter in a case of cerebral malaria.

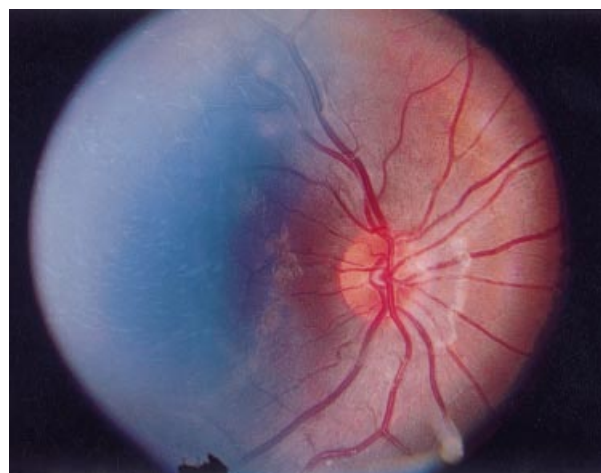


Figure 4. Papilloedema in a patient of cerebral malaria.

when present in a child in coma, may be a clinical sign for diagnosis of cerebral malaria in a setting where we have to differentiate it from other conditions.

Our findings regarding retinal haemorrhages are different from those of Lewallen *et al.*⁷ in which they were present in 19 (33.92%) out of 56 cerebral and 1 (2%) out of 50 non-cerebral malaria patients ($p < 0.001$). Similarly, studying the trend of mortality in patients with retinal haemorrhages, Allen *et al.*¹⁹ in a study of 70 patients, observed retinal haemorrhages in 20 patients of whom 14 died and only six survived. Searching the Indian literature did not reveal any report of retinal haemorrhages in a significant number of patients.^{15,16,17,20}

In this study, retinal haemorrhage was not associated with increased mortality either in cerebral malaria or non-cerebral malaria. Indeed, three patients with retinal haemorrhage who also had bilateral papilloedema, and two patients who had retinal haemorrhage with blurred disc margins, all recovered completely without any neurological sequelae. There was a significant association of retinal haemorrhage with cerebral malaria and severe non-cerebral malaria as compared to uncomplicated malaria ($p < 0.01$), and the values were highly significant in patients with both severe anaemia and falciparum malaria as compared to other pernicious syndromes ($p < 0.001$), but was not associated with significantly greater mortality.

Papilloedema

Papilloedema was present in 17 (7.94%) patients of cerebral malaria, of whom three also had associated retinal haemorrhages. Only three (17.64%) patients with papilloedema died, compared to an overall mortality of 21.49% in patients of cerebral malaria. Two patients with uncomplicated malaria also had papilloedema and recovered completely, while none of the patients with severe non-cerebral malaria had papilloedema. Thus, although the papilloedema was not associated with mortality in patients of cerebral malaria, its association with cerebral malaria was highly significant ($p < 0.001$) when compared to non-cerebral malaria patients. These findings are quite different from those of Looareesuwan *et al.*⁹ who reported papilloedema in only one of 144 patients with cerebral malaria and those of the 1990 WHO report,¹² according to which papilloedema is not a feature of cerebral malaria. Our findings are also different from that of Lewallen *et al.*^{7,8} who found relative risks of poor outcome/death in children with papilloedema of 5.2-fold and 6.2-fold in their 1993 and 1996 studies, respectively; furthermore, none of their patients with non-cerebral malaria had papilloedema, whereas in this study two such patients had papilloedema. According to Lewallen

et al., marked increase in ICT probably reflected as papilloedema and extramacular oedema.⁸ Surveying the Indian studies our findings are similar to Padahiary²⁰ but in disagreement with Dhamija *et al.*¹⁷

Disc pallor

The most important observation of this study was the presence of disc pallor in five (2.33%) patients with cerebral malaria, which included one patient who had associated blurring of disc margins. Four of the five died. We found similar lesions in seven patients of the non-cerebral malaria group (6 uncomplicated, one severe non-cerebral malaria), but there were no deaths. Disc pallor was thus a predictor of outcome in patients of cerebral malaria ($p < 0.05$). We did not come across this observation in any of the previous studies. All these patients with cerebral malaria had haemoglobin level < 3.0 g%, and jaundice. One patient also had renal failure, so probably it reflected the mortality trend of severity of anaemia and other pernicious syndromes. Earlier, we had observed high mortality ($> 82\%$) in patients having three or more pernicious syndromes together.²⁴

Retinal oedema

Retinal oedema was found in six patients with cerebral malaria. It was associated with coexisting hyperaemia of the disc, and with blurred disc margins, in one patient each. Only one patient with retinal oedema died. Four patients with severe non-cerebral malaria and one patient with uncomplicated malaria also had retinal oedema, and all of them recovered completely. The mortality in patients with retinal oedema was 16.66%, vs. 21.46% in patients of cerebral malaria as a whole. These findings are different from those of Lewallen *et al.*^{7,8} in which extramacular oedema was associated with relative risk of poor outcome, 3.9-fold in 1993 and 2.9-fold in 1996. There is no mention of relative risk of retinal oedema in other studies.

Blurred disc margins

Blurred disc margins were found in 25 (11.68%) patients of cerebral malaria. It was associated with disc hyperaemia in five patients, retinal haemorrhage in two, retinal oedema in one and disc pallor in another. Three patients with blurred disc margins not associated with any other retinal findings expired. This mortality was not statistically significant. Blurred disc margins were also present in seven patients with non-cerebral malaria (two with severe non-cerebral malaria and five of uncomplicated malaria) and all recovered completely.

Vitreous haemorrhage

Vitreous haemorrhage was present in one patient with cerebral malaria associated with severe anaemia (Hb 4.5 g%).²⁵ This patient initially presented with blindness before developing unconsciousness, and died after 3 days of standard antimalarial and other supportive treatment. Vitreous haemorrhage can also be a cause of sudden blindness in patients of falciparum malaria besides cortical blindness^{26,27} and retrobulbar neuritis.²⁸

Exudate

Hard exudate was present in one (0.46%) patient with cerebral malaria who recovered completely. According to WHO (1990),¹² exudates are rarely found in cerebral malaria, while Looareesuwan *et al.* described soft exudates in two patients.⁹

Conclusions

To conclude, different types of retinal changes are commonly seen in plasmodium falciparum malaria. Haemorrhages and papilloedema are found more frequently in cerebral malaria than in severe non-cerebral and uncomplicated malaria, but are not associated with increased mortality. The presence of disc pallor may be associated with increased mortality in cerebral malaria.

References

- Nosten F, Price RN. New antimalarials, a risk benefit analysis. *Drug Saf* 1995; **12**:264–73.
- Baum MJ, Va Der Kaay HJ. Epidemic malaria in India and El Nino Southern Oscillation. *Lancet* 1994; **334**:1638.
- Tyagi BK. Malaria in Thar desert. A critical review. *ICMR Bull* 1995; **25**:85–90.
- Poncet F. De la retino choroidite palustre. *Ann d'Oculistique* 1879; **79**:201–18.
- Smith H. Night blindness. *Trans Ophthalmol Soc UK* 1906; **24**:135–41.
- Bywater HH. Notes on malaria conditions of the eyes. *Trans Ophthalmol Soc UK* 1922; **42**:359–69.
- Lewellan S, Taylor TE, Molyneux ME, Wills BA, Courtright P. Ocular fundus findings in Malawian children with cerebral malaria. *Ophthalmology* 1993; **100**(6):857–61.
- Lewallen S, Bakker H, Taylor TE, Wills BA. Retinal findings predictive of outcome in cerebral malaria. *Trans R Soc Trop Med Hyg* 1996; **90**(2):144–6.
- Looareesuwan S, Warrell DA, White NJ, *et al.* Retinal haemorrhage. A common sign of prognostic significance in cerebral malaria. *Am J Trop Med Hyg* 1983; **324**:911–15.
- Haslett P. Retinal haemorrhages in Zambian children with cerebral malaria. *J Trop Ped* 1991; **37**:86–7.
- Kayembe D, Maertens K, De Laey JJ. Ocular complications of cerebral malaria. *Bulletin de la Society Belge d'Ophthalmologic (Gent)* 1980; **190**:53–60.
- Warrell DA, Molyneux ME, Beales P. World Health Organization: severe and complicated malaria. *Trans Roy Soc Trop Med Hyg* 1990; **84**(Suppl. 2):1–65.
- World Health Organization. Management of severe and complicated malaria: A practical handbook. London, World Health Organization Graphics, 1991.
- Davis MW. The significance of retinal haemorrhages in cerebral malaria. *Am J Trop Med Hyg* 1984; **33**:1287–8.
- Gopinathan VP, Ganguly SD, Chivukula LK. Cerebral malaria. A clinicopathological study. *JAPI* 1986; **34**:473–5.
- Gupta A, Malhotra HS, Bombery P. Clinical pattern of complicated malaria in North-West India. *JAPI* 1987; **35**:15.
- Dhamija RM, Banerjee AK, Venkataraman S. Cerebral malaria. *Prog Clin Neurosci* 1989; **5**:315.
- Molyneux ME, Taylor TE, Wirima JJ. Clinical features and prognostic indicators in paediatrics cerebral malaria. *Q J Med* 1989; **71**:441.
- Allen SJ, O'Donnell A, Alexander NDE, Clegg JB. Severe malaria in children in Papua New Guinea. *Q J Med* 1996; **89**:779–88.
- Padhiary KN, Behera GB, Parida GN, Das SP. Neurological complications of falciparum malaria; *JAPI* 1996; **44**(12):910–11 (Abstract).
- Elliott RH. *Tropical Ophthalmology*. London, Oxford University Press, 1920.
- Rubenstein RA, Yanoff M, Albert DM. Thrombocytopenia, anaemia, and retinal haemorrhages. *Am J Ophthalmol* 1968; **65**(3):435–9.
- Holt JM, Gordon Smith EC. Retinal abnormalities in diseases of the blood. *Br J Ophthalmol* 1969; **53**:145–60.
- Kochar DK, Kumawat BL, Shubhakaran, Kochar SK, Agarwal RP. Severe and Complicated Malaria in Bikaner (Rajasthan), Western India. *SEAJ Trop Med Hyg* 1997; **28**:259–67.
- Kochar DK, Shubhakaran, Kochar SK, Vyas SP. Vitreous haemorrhage in falciparum malaria. *JAPI* 1997; **45**:670.
- Schmutzhard E, Gerstenbrand F. Cerebral malaria in Tanzania. Its epidemiology, clinical symptoms and neurological long term sequelae in the light of 66 cases. *Trans Roy Soc Trop Med Hyg* 1984; **78**:351.
- Bondi FS. The incidence and outcome of neurological abnormalities in childhood cerebral malaria. A long term follow-up of 62 survivors. *Trans Roy Soc Trop Med Hyg* 1992; **86**:17–19.
- Wadia PZ. Retrobulbar neuritis in two patients with falciparum malaria. *JAPI* 1992; **38**(10):800–1.