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Original Research Article

Prevalence of Malarial Retinopathy in Adults and its Prognostic Significance

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Abstract:

Introduction: Malarial retinopathy is a set of retinal signs in severe malaria due to falciparum malaria. It includes papilloedema, retinal hemorrhages, blurred disc margins, retinal whitening, retinal edema, vascular changes and soft exudates.

Materials & Methods: This prospective study included retinal examination of 124 adult malaria patients admitted to tertiary care hospital. Retinal haemorrhages and vascular changes, papilloedema, peripheral whitening, and blurring of the disc borders were noted,

Results: Prevalence of malarial retinopathy was 22.58%. Retinal hemorrhages was the most common feature (88.5% in severe malaria, 0.0% in uncomplicated malaria, 95.6% in cerebral severe malaria, 50.0% in non-cerebral severe malaria). Papilloedema was also significantly higher in cerebral malaria (81.8%) and non-cerebral malaria (25.0%). The case fatality rate of our study was higher (severe malarial - 42.9%, cerebral malaria - 50.0%). Papilloedema (p-0.009), renal failure (p-0.002) and serum lactate level (p-0.001) were significantly associated with mortality.

Conclusion: Malaria retinopathy is very common in adults with severe malaria, particularly cerebral malaria. When compared to severe non-cerebral malaria, cerebral malaria is more likely to cause haemorrhage and papilloedema. Papilloedema, lactic acidosis, and renal failure all significantly increase the risk of death.

Keywords: Cerebral malaria, lactic acidosis, malarial retinopathy, mortality, papilloedema.

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Introduction

Malaria is one of the most important mosquito-borne infectious diseases. Every year more than one million people die from severe malaria. Several organs can be affected in complicated malaria, as well as eye.[1] The most severe neurological complication of falciparum malaria is Cerebral malaria (CM) and has acase fatality rate (CFR) of up to 15%.[2,3] Because of the similarity of the cerebral and retinal microvasculatures, the retinal circulation has been researched as a surrogate for the cerebral circulation to investigate cerebral malaria.[2] Malarial retinopathy includes papilloedema, retinal hemorrhages, blurred disc margins, retinal whitening, retinal edema, vascular changes and soft exudates. Of these, retinal whitening and vascular changes are specific to cerebral malaria.[3,4] On histopathological examination, vessel changes and discoloration have been linked with sequestration of pRBCs, and retinal whitening has been shown to be caused by local tissue hypoxia.[9,10] Additionally, the presence and severity of malarial retinopathy (MR) is associated with parasite sequestration in the brain, prolonged coma, and death.[7,11,12] Although retinal haemorrhages have also been documented [8], other aspects of malarial retinopathy need indirect ophthalmoscopy or other, less well-studied methods. Because malaria-specific retinal whitening and vascular discoloration can be more pronounced in the peripheral retina and may not be visible in the field by a non-expert using a direct ophthalmoscope, the precise ophthalmoscopic approach used is crucial.[4] High interobserver agreement exists when using indirect

ophthalmoscopy to grade the seriousness of results, including retinal whitening.[5]

Materials & Methods

This prospective study was carried out at Ophthalmology department with collaboration of Medicine department of tertiary care hospital of Gujarat after getting approval from institutional ethical committee. Consecutive adult patients (>18 years) with severe or uncomplicated falciparum malaria were recruited. Written informed consent was obtained from each patient or attending relative. Exclusion criteria were: patients unable or unwilling to co-operate with eye examination; contraindications to tropicamide eye drops, such as angle closure glaucoma or documented allergy; and patients with severe corneal scarring or cataracts in both eyes precluding ophthalmoscopy and retinal photography, diabetes, malignancy.

A patient was diagnosed with cerebral malaria if their Glasgow Coma Score was less than 11 and there was no other clear cause for their coma. Complete blood counts, haemoglobin, parasitaemia, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, and glucose levels were examined as part of the laboratory analysis. The examination of the eyes comprised direct and indirect ophthalmoscopy, pupillary accommodation and response to light. Within 30 minutes of administering two drops of tropicamide at 0.5% or 1%, an ophthalmoscopy was performed. In addition, all patients had digital photographs taken of both retinas whenever possible. Haemorrhages and vascular changes, papilloedema, peripheral whitening, and blurring of the disc borders were noted. According to Beare et al.[5] and Harding et al.[6] classification, retinopathy was evaluated as mild, moderate, or severe. Grading is determined by: the size of the affected area of retinal whitening relative to the optic disk; number of retinal haemorrhages and proportion of these haemorrhages that are white centred; the extent of vessel discolouration; and the severity of papilloedema.

Statistical analysis

Data was analysed with Epi info version 7.1.4.0 software. Quantitative data was described as mean and standard deviation (SD); Qualitative data was described as frequency and percentage. Comparison of categorical data was analysed with Chi square. p value less than 0.05 was considered as significant.

Results

Table 1: Age and gender wise distribution of malaria patients

Characteristics	Severe (n-29)	Uncomplicated (n-95)	Total (n-124)
Age	39.12 ± 8.71	32.23 ± 7.89	38.12 ± 7.23
Gender			
Male	22 (75.9%)	73 (76.8%)	95 (76.6%)
Female	7 (24.1%)	22 (23.2%)	29 (23.4%)

Over a period of one year, total 124 malaria cases were enrolled in the study. Mean age was 38.12 ± 7.23 years. Majority of the patients (58, 46.8%) was in 31 to 40 year age group. About 95 patients (76.6%) were male.

Table 2: Severity of malarial retinopathy in patients

Type of Malaria	Retinopathy	Mild	Moderate	Severe
Uncomplicated (n-85)	2 (2.4%)	2 (100)	0 (0.0%)	0 (0.0%)
Severe (n-39)	26 (66.7%)	7 (26.9%)	9 (34.6%)	10 (38.5%)
Cerebral (n-28)	22 (78.5%)	5 (22.7%)	7 (31.8%)	10 (45.5%)
Non cerebral (n-11)	4 (36.4%)	2 (50.0%)	2 (50.0%)	0 (0.0%)
Total (n-124)	28 (22.6%)	9 (32.1%)	9 (32.1%)	10 (35.7%)
p value: Uncomplicated v/s severe malaria	< 0.001	0.03		
p value: Cerebral v/s Non –cerebral	0.01	0.25		

Prevalence of malarial retinopathy was 22.58% (28/124). Malarial retinopathy was present in 66.7% patients (26/39) with severe malaria, 78.5% patients (22/28) with cerebral malaria, 36.4% patients (4/11) with non-cerebral malaria, 2.4 % patients (2/85) with uncomplicated malaria. Prevalence of malarial retinopathy was significantly higher in severe malaria than uncomplicated malaria (p< 0.001) and also higher in cerebral malaria as compared to non-cerebral malaria (p -0.01).

Proportion of moderate to severe retinopathy was 73.0% (19/26) in severe malaria, 77.3% (17/22) in cerebral malaria.

Proportion of moderate to severe retinopathy was significantly higher in severe malaria than uncomplicated malaria (p – 0.03) but not significantly different between cerebral malaria, non-cerebral malaria and severe malaria (p -0.25).

Table 3: Distribution of patients according to retinal findings and mortality

Malaria retinopathy	Retinal haemorrhage	Papil-loedema	Whitening peripheral retina	Mortality
Uncomplicated (n-2)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe (n-26)	23 (88.5%)	19 (73.1%)	7 (26.9%)	12 (46.2%)
Cerebral malaria (n-22)	21 (95.6%)	18 (81.8%)	6 (27.3%)	11 (50.0%)
Non cerebral (n-4)	2 (50%)	1 (25.0%)	1 (25.0%)	1 (25.0%)
Total (n-28)	23 (82.1%)	19 (67.8%)	7 (25.0%)	12 (42.9%)
p value: Uncomplicated v/s severe malaria	0.02	0.09	1.00	0.48
p value: Cerebral v/s Non –cerebral	0.04	0.04	1.00	0.59

Retinal hemorrhages was the most common feature present in 88.5% cases of severe malaria (23/26). Out of 23 patients with retinal hemorrhages, 20(86.9%) had severe anaemia (p -0.02).Papilloedema was present in 73.1% cases of severe malaria (19/26) and 81.8% cases of cerebral malaria (18/22), and 25.0% cases of non cerebral malaria (1/4). Retinal whitening was seen in 25.0% patients (7/28). All these 7 patients had severe malaria. Out of 7 patients, 6 had cerebral malaria.

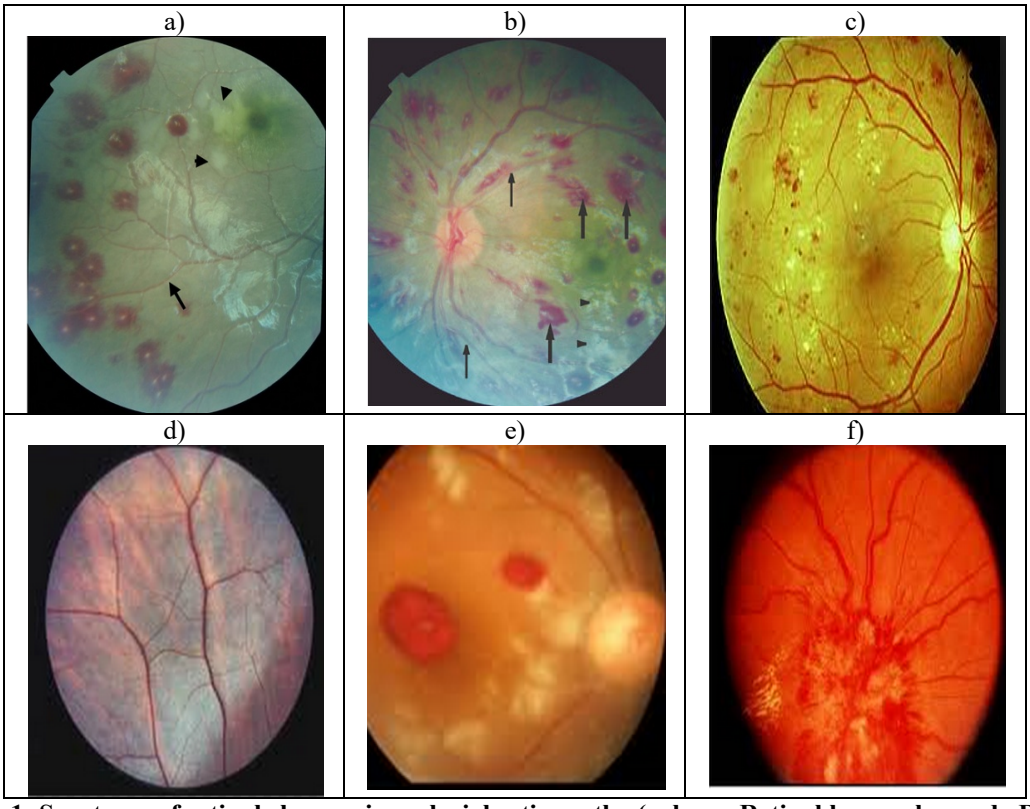

Figure 1: Spectrum of retinal changes in malarial retinopathy (a, b, c – Retinal hemorrhage; d –Retinal whitening; e, f - Papilloedema

Table 4: Comparison of various variables between survived and died patients

Variables	Survived (n-16)	Died (n-12)	p value
Retinal haemorrhage (n-240	13 (81.3%)	11 (91.7%)	0.231
Whitening peripheral retina (n-7)	2 (12.5%)	5 (41.7%)	0.102
Papilloedema (n-15)	5 (31.2%)	10 (83.3%)	0.009
Severe anaemia (n-24)	12 (75.0%)	12 (100%)	0.112
Renal failure (n-17)	6 (37.5%)	11 (91.7%)	0.002
Serum lactate	65.35 ± 14.23	49.46 ± 10.67	0.001

Mortality rate in malarial retinopathy was 42.9% (12/28). All cases had severe malaria. Out of 12 severe malaria patients, 11 had cerebral malaria. Retinal haemorrhage, whitening peripheral retina and severe anaemia were not significantly associated with survival of patients. Papilloedema (p-0.009),

renal failure (p-0.002) and serum lactate level (p-0.001) were significantly associated with mortality. Lactate level was also significantly higher in moderate to severe retinopathy as compared to mild retinopathy.

Discussion

In the present study, prevalence of malarial retinopathy was 22.58%. This result differs from previous studies on malarial retinopathy in adults describing lower prevalence.[7–9] In the present study, prevalence of malarial retinopathy was significantly higher in severe malaria (66.7%) than uncomplicated malaria (2.4%, $p < 0.001$) and also higher in cerebral malaria (78.5%) as compared to non-cerebral malaria (36.4%, p -0.01). In the study of Maude RJ et al.[10], retinopathy was seen in 43% of people with non-cerebral malaria, 70% of adults with cerebral malaria, 63% of adults with severe malaria, and 60% of adults with uncomplicated malaria. Kochar DK et al.[9-11] had found retinopathy in 34% cases of cerebral malaria, 24% cases of non-cerebral severe malaria, and 12% cases of uncomplicated malaria. Another study on adults with severe falciparum malaria in Bangladesh found retinal changes to be present in 70.0% patients with cerebral malaria, 42.8% patients with non-cerebral severe malaria, and 20.0% patients with uncomplicated malaria.[2]Other studies found lower prevalence of retinopathy in uncomplicated malaria than our study.[2,7,9]

In the present study, proportion of moderate to severe retinopathy was significantly higher in severe malaria than uncomplicated malaria (p – 0.03) but not significantly different between cerebral malaria, non-cerebral malaria and severe malaria (p -0.25). In the study of Maude RJ et al.[10], moderate or severe retinopathy was 55% in cerebral malaria, 14% in non-cerebral malaria, 44% in severe malaria, and 20% in uncomplicated malaria.

In the present study, retinal hemorrhages was the most common feature present in 88.5% cases of severe malaria which was significantly higher than uncomplicated malaria (0.0%, p -0.02). It was commonly observed in cerebral severe malaria than non-cerebral severe malaria. Severity of anaemia was also significantly associated with retinal hemorrhages (p -0.02).Retinal haemorrhages have been proposed to be visual signs of vascular lesions implicated in the development of this disorder since it has been established that their existence is connected with severity indicators, particularly in cerebral malaria.[8] In P. falciparum patients, sequestration of parasitized RBCs and cytoadhesion with rosetting are major pathogenic mechanisms that cause retinal haemorrhage. The presence of accompanying anaemia and thrombocytopenia may contribute to the development of retinal haemorrhage. ElliottRH et al.[12] and Kayembe D et al.[13] have noted that in malaria patients, severe anaemia is correlated with retinal haemorrhages.

In the present study, Papilloedemawasalso significantly higher in cerebral malaria (81.8%) and non-cerebral malaria (25.0%). However, retinal whitening was also not different among cerebral malaria (27.3%), and 50.0% cases of non-cerebral malaria (25.0%). In the study of Maude RJ et al.[10], retinal hemorrhages was present in 55% of cerebral malaria, 52% of severe malaria, 47% of uncomplicated malaria. Papilloedema was present in 5% of cerebral malaria and 7% in severe malaria. Retinal whitening was seen in 50% of cerebral malaria, 48% of severe malaria and 20% of uncomplicated malaria.

The pathogenesis of severe and cerebral malaria in adults and children is currently under discussion.14 The pathophysiology of acidosis, coma, mortality, and neurological impairment in both groups is thought to be significantly influenced by the obstruction of microcirculatory blood flow by sequestered infected erythrocytes and other variables.[15] Additionally, fatal occurrences of intravascular fibrin clots and leukocyte and platelet buildup in children have been recorded.[16] Although there was no vessel discoloration seen in the current investigation, the spectrum of malarial retinopathy was identical to that previously described in children from Africa.[3] The dehaemoglobinization of stationary erythrocytes infected with adult parasites in blocked capillaries, arterioles, and venules is assumed to be the cause of vessel discoloration.[16] In the present study, the spectrum of malarial retinopathy was similar to that previously described in African children, but no vessel discolouration was observed.[3] Vessel discolouration is thought to be due to dehaemoglobinisation of stationary erythrocytes infected with mature parasites in obstructed capillaries, arterioles and venules.[16] It is unlikely that this was caused by the different technique since it has been shown previously that blood vessel discolouration in patients with severe malaria is seen easily on retinal photographs.[3,4,5,16]

The case fatality rate of our study (severe malarial - 42.9%, cerebral malaria - 50.0%) was significantly higher than previously reported studies which were around 13-22%. because of variation of study population.[17,18] In the present study, retinal haemorrhage, whitening peripheral retina and severe anaemia were not significantly associated with mortality of patients. However, papilloedema (p-0.009), renal failure (p-0.002) and serum lactate level (p-0.001) were significantly associated with mortality. Lactate level was also significantly higher in moderate to severe retinopathy as compared to mild retinopathy. Chaudhari KS et al.[19] reported higher mortality rate in patients with retinal whitening (23.07%), with vessel changes (18.75%), with retinal hemorrhage (11.11%) and with hyperlactatemia (18.46%), respectively.

Lactic acidosis (lactate >45 mg/dl) raises mortality rates and is linked to anaemia and respiratory distress.[20,21]High parasite densities or metabolic acidosis brought on by hypoxia in host tissues can both cause a rise in serum lactate. The main factor is hypoxia, which is brought on by adhering parasitized red blood cells (RBCs) obstructing the microvasculature.[20] Due to decreased absorption of antimalarial medications by infected erythrocytes and increased cytoadherence of infected erythrocytes to capillary endothelium, lactic acidosis might have a fatal outcome.[22,23]

Conclusion

Malaria retinopathy is very common in adults with severe malaria, particularly cerebral malaria. When compared to severe non-cerebral malaria, cerebral malaria is more likely to cause haemorrhage and papilloedema. Presence of malarial retinopathy confirms a diagnosis of severe malaria. Papilloedema, lactic acidosis, and renal failure all significantly increase the risk of death. The absence of retinal vessel changes in adults was conspicuous and may indicate a difference in the calibre of vessels involved in sequestration between adults and children.

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