

Retinopathy as a Prognostic Marker in Cerebral Malaria

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Received: September 22, 2015;

Initial review: September 23, 2015;

Accepted: February 13, 2016.

Objectives: To study the association between fundal changes (malarial retinopathy) and mortality in children with cerebral malaria.

Methods: 50 consecutive children (mean age 8.4 y, 23 males) with cerebral malaria (acute febrile encephalopathy and either peripheral smear or Rapid diagnostic test positive for malaria) were evaluated by a single ophthalmologist for any changes of retinopathy. Children were managed as per standard guidelines for treatment of cerebral malaria.

Results: *P. vivax* infection was seen in one child, *P. falciparum* infection in 42 children, and a mixed infection in 7. Retinopathy was present in 48% of the children. 13 children died during hospital stay. The mean interval from admission to fundus examination was 11.6 (4.64) h. Presence of 'any retinopathy' ($P=0.02$), and either of papilledema ($P=0.02$), hemorrhages ($P=0.005$) or vessel changes ($P=0.01$), were associated with a significantly higher risk of death.

Conclusions: Malarial retinopathy is significantly associated with mortality in children with cerebral malaria. It may be used for both prognostication, and triaging for optimum utilization of intensive care facilities in these children.

Keywords: Eye-examination, Febrile encephalopathy, Fundal changes, Malarial retinopathy, Outcome.

Malarial retinopathy includes blurred disc margins, papilledema, retinal hemorrhages, retinal whitening, retinal edema, vascular changes and soft exudates [1]. Of these, retinal whitening and vascular changes are specific to cerebral malaria. The detection of malarial retinopathy has been shown to be associated with a poorer prognosis [2]. In this prospective cohort study, we studied the association between fundal changes (malarial retinopathy) and mortality in children with cerebral malaria admitted in a medical college hospital.

METHODS

The study was carried out in the Department of Pediatrics, SS Medical College and associated GM Hospital, Rewa, Madhya Pradesh during the period of August 2013 to July 2014, after clearance from the Institutional Ethical Committee. This area is classified under hyper-endemic zone for malaria [3,4]. A convenience sample size of 50 children was decided, and consecutive children aged between 6 months and 18 years presenting with febrile encephalopathy (fever and altered sensorium or coma at the time of admission with Glasgow Coma Scale ≤ 10 , with or without seizures) and having

malaria positivity based on presence of asexual form of plasmodium on peripheral smear and/or rapid diagnostic test positive were considered eligible for inclusion.

A detailed clinical evaluation including history and examination was carried out for all study participants at the time of admission. Blood sugar estimation (glucose-strip), complete blood counts, and blood culture were done at admission in all children. By using aseptic precautions, finger prick sample of blood was collected to prepare thick and thin smear of blood on glass slides, and evaluated for presence of any malarial parasite under oil-immersion, as per standard procedures. Subsequently, all investigations required for clinical management were done by the concerned treating physicians. Rapid diagnostic test used was Wondfo Malaria: One step Pf Malaria Test (Guangzhou Wondfo Biotech Co. Limited China; supplied by the Government of India), performed as per manufacturer's instructions.

Fundus examination was performed by a single ophthalmologist in all patients, after pupils were fully dilated using mydriatic eye drops; photographs of the fundus were taken by fundus camera (Topcon). Presence of papilledema, hemorrhages and vessel changes,

peripheral whitening, and blurring of disc margins were noted and recorded separately, in addition to any other ophthalmologic abnormality. Presence of either of these was labelled as 'Any retinopathy' for the purpose of statistical analysis.

In unconscious patients, vitals, Glasgow Coma Score and blood sugar were recorded until they became conscious or died. Initially, it was done every 6 hours for first 24 hours then every 12 hours until they became conscious. In patients who were hypoglycemic (blood sugar <40mg/dL) at the time of admission, blood sugar, vitals, and coma score were recorded hourly until their blood sugar normalized.

Statistical analysis: The data were entered and analyzed using the software Microsoft Excel 2013 for Windows, and online MedCalc software (<https://www.medcalc.org>). Appropriate univariate and bivariate analyses were carried out using the Student t test for the continuous variable / proportion test (z test / t test) and two-tailed Fisher exact test or chi-square test for categorical variables. The critical levels of significance of the results were considered at 5%.

RESULTS

A total of 57 consecutive children were approached; seven children were excluded as they had features suggestive of other conditions causing febrile encephalopathy along with malaria. There were 50 children (24 males) with mean (SD) age of 8.4 (3.96) years. The mean interval from admission to fundus examination was 11.6 (4.64) hours. *P. vivax* infection was seen in one child, *P. falciparum* in 42 children, and a mixed infection in seven children. Any retinopathy was present in 24 (48%) of the study children.

There were 13 deaths (26%) during the hospital stay. Among children with cerebral malaria, presence of 'any retinopathy' ($P=0.02$), and either of papilledema ($P=0.02$), hemorrhages ($P=0.005$), vessel changes ($P=0.01$), were associated with a significantly higher risk of death (**Table I**).

Multivariate logistic regression analysis showed that papilledema, hemorrhage, and vessel changes were significantly associated in predicting the mortality, while peripheral whitening and margin were insignificant. Further, on next step of regression, only factor hemorrhage showed a significant independent association ($P=0.002$).

DISCUSSION

This hospital-based study of 50 children with cerebral malaria documented malarial retinopathy in 48% children; it was associated significantly with mortality. Multivariate logistic regression analysis showed only retinal hemorrhages to have a significant independent association.

The lacunae of the present study include a sample size of convenience, absence of a comparator group, inclusion of children with non-falciparum malaria, and non-inclusion of other patient/disease characteristics (GCS, age, parasite density, metabolic abnormalities) in the multivariate analysis. There is high occurrence of retinopathy, particularly retinal whitening (suggestive of retinal ischemia) in non-cerebral severe malaria also [1]; thus, it may not be possible to associate malarial retinopathy with mortality in cerebral malaria in children from other non-cerebral severe malaria. However, being the first such study in children, consecutive enrolment of all patients, and ophthalmoscopy by a single trained examiner were some of the strengths of the study.

Previous studies in both children (26.7%) [5] and adults (21%) [1] have reported mortality rates similar to the present study. In children with cerebral malaria, the rates of malarial retinopathy reported in the literature vary from 61%-79% [2,6], which are much higher than those in the present study. Mortality in children with any retinopathy was 41.7%, as compared to 21-24% reported previously in adults and children [1,2]. Retinal hemorrhages, suggested to be the visible evidence of vascular lesions involved in the pathogenesis of cerebral malaria [7], were present in a similar proportion of

TABLE I OPHTHALMOLOGICAL FINDINGS AND MORTALITY IN CHILDREN WITH CEREBRAL MALARIA (N=50)

Characteristics	Died (n=13), No. (%)	P value	OR (95% CI) of Death
Any retinopathy	10/24 (41.7)	0.02	5.5 (1.3, 23.4)
Papilledema	6/11 (54.5)	0.02	5.5 (1.3, 23.2)
Hemorrhages	6/9 (66.7)	0.005	9.7 (1.9, 48.)
Vessel changes	6/10 (60)	0.01	7.1 (1.6, 31.9)
Peripheral whitening	1/1 (100)	0.18	9.0 (0.3, 235.4)
Blurring of disc margins	6/13 (46.1)	0.06	3.7 (0.9, 14.4)

WHAT THIS STUDY ADDS?

- Malarial retinopathy is significantly associated with mortality in children with cerebral malaria in Central India.

children with cerebral malaria in our study as in previous reports (18% vs. 22%) [1,5]. The mortality in children with retinal hemorrhages in our study (66.7%) was much higher than previous studies *viz.*, 37.5% in children [8] and 20% in adults [1]; though similar to an older study by Allen, *et al.* [9].

Fundoscopy is an easily acquired skill that can be done at the bedside. The significant association of malarial retinopathy with mortality in children with cerebral malaria may help pediatricians in using fundoscopy findings to prognosticate affected families, and by prioritizing intensive care services for these children, may also ensure better utilization of healthcare resources.

Acknowledgement: Mr. Arvind Kavishwar, Bio-statistician, Regional Medical Research Center for Tribals (ICMR), Jabalpur, MP for help in statistical analysis.

Contributors: JS: conceived and planned the study, and supervised the conduct of the study and preparation of the manuscript; RV: enrolled subjects, collected and analyzed the data, and prepared the initial draft of the manuscript; AT: carried out the ophthalmological examination and was involved in the study planning and manuscript preparation; HPS, DM: assisted in the planning of the study and preparation of the manuscript. All authors approved the final manuscript.

Funding: ICMR financial assistance for MD thesis.

Competing interest: None stated.

REFERENCES

1. Kochar DK, Shubakaran, Kumawat BL, Thanvi I, Joshi A, Vyas SP. Ophthalmoscopic abnormalities in adults with falciparum malaria. *QJ Med.* 1998;91:845-52.
2. Beare NA, Southern C, Chalira C, Taylor TE, Molyneux ME, Harding SP. Prognostic significance and course of retinopathy in children with severe malaria. *Arch Ophthalmol.* 2004;122:1141-7.
3. Jain V, Avinash C, Pradeep K, Manmohan S, Mrigendra P, Rasik B, *et al.* Burden of cerebral malaria in Central India (2004–2007). *Am J Trop Med Hyg.* 2008;79:636-42.
4. Singh J, Soni D, Mishra D, Singh HP, Bijesh S. Placental and neonatal outcome in maternal malaria: A prospective cohort study from Central India. *Indian Pediatr.* 2014;51:285-8.
5. Schemann J, Doumbo O, Malvy D, Traore L, Kone A, Sidibe T, *et al.* Ocular lesions associated with malaria in children in Mali. *Am J Trop Med Hyg.* 2002; 67:61-3.
6. Birbeck G, Beare N, Lewallen S, Glover SJ, Molyneux ME, Kaplan PW, *et al.* Identification of malaria retinopathy improves the specificity of the clinical diagnosis of cerebral malaria: findings from cohort study. *Am J Trop Med Hyg.* 2010; 82: 231-4.
7. Looareesuwan S, Warrell D, White N, Chanthavanich P, Warrell M, Chantaratherakitti S, *et al.* Retinal hemorrhage, a common sign of prognostic significance in cerebral malaria. *Am J Trop Med Hyg.* 1983; 32:911-5.
8. Molyneux M, Taylor T, Wirima J, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: A study of 131 comatose Malawian children. *QJ Med.* 1989;71:441-59.
9. Allen S, O'Donnell A, Alexander N, Clegg J. Severe malaria in children in Papua New Guinea. *QJM.* 1996; 89:779-88.