To Study the Association of Retinopathy with Plasmodium Species in Children’s with Cerebral Malaria

Authors
Dr Puneet Agrawal¹, Dr Jyoti Singh², Dr Sujata Lakhtakia³
¹Senior Resident, Department of Pediatrics, S.S. Medical College, Rewa
²Professor and Head, Department of Pediatrics, S.S. Medical College, Rewa
³Assistant Professor, Department of Ophthalmology, S.S. Medical College, Rewa
Corresponding author
Dr Puneet Agrawal
Room no.8, PG Boys Hostel, S.S. Medical College, Rewa (M.P.), Pin – 486001 INDIA
Phone: 9425721482, Email: dr.puneetagrawal@gmail.com

Abstract
Objectives: To study the association of retinopathy with plasmodium species in children’s with cerebral malaria
Design: Prospective, observational, cohort study. Cohort study comprising of all malaria positive patients.
Setting: Study was carried out in Department of Paediatrics, S.S.M.C and associated G.M. Hospital Rewa, Madhya Pradesh during the period of 1st August 2015 to 31st July 2016.
Participants: 100 consecutive patients with cerebral malaria evaluated by ophthalmologist for changes of retinopathy were included in the study. All 100 cases were malaria positive.
Results: In cerebral malaria out of 100 cases, 12 cases were Plasmodium vivax positive, 74 cases are Plasmodium falciparum positive, and 14 cases are both Plasmodium vivax and Plasmodium falciparum positive. Out of total 41 cases of retinopathy maximum cases were Plasmodium falciparum positive (78%), Plasmodium vivax is positive in 2.5% of cases. While 19.5% cases were both pv and pf positive.
Conclusions: Malarial retinopathy is significantly associated with P.falciparum species of malarial parasite in children with cerebral malaria indicating P.falciparum as the most important cause of cerebral malaria or serious disease.
Keywords: Cerebral Malaria, Retinopathy, Plasmodium vivax, Plasmodium falciparum.

Introduction
Malaria is a mosquito-borne infectious disease caused by a eukaryotic protist of the genus plasmodium¹ that is widespread in tropical and subtropical regions². There are four types of malarial³ parasite namely; P.falciparum, P. vivax, P.ovale and P.malariae. Recently, fifth type P. knowlesi (a primate malarian species) was also shown to cause malaria in human. Among these P.falciparum, P. vivax are the most importantly species responsible for causing malaria. Cerebral malaria appears to be one of the most common non-traumatic encephalopathy in the world⁴. Cerebral malaria can be fatal in the absence of prompt recognition of the disease and its complication, and in the absence of active appropriate management of patients, especially in
the high risk groups like pregnant women and young children. Cerebral malaria is thought to be caused only by P.falciparum but now P. vivax has also been seen to cause cerebral malaria. The pathogenesis of coma in cerebral malaria remains poorly understood. Obstruction of the brain microvasculature because of sequestration of parasitized red blood cells is one of the mechanisms that could contribute to coma [5–9]. The retina provides a unique opportunity to observe the central nervous system vasculature and therefore to study cerebral vasculature directly i.e. eye being regarded as an extension of the brain. The detection of malarial retinopathy can be a good diagnostic tool for cerebral malaria. Malarial retinopathy acts as a marker of serious disease. This area of Madhya Pradesh is classified under hyper endemic zone for malaria [10,11].

Objective
To study the association of retinopathy with plasmodium species in children’s with cerebral malaria

Methodology
The study was carried out in the Department of Pediatrics, SS Medical College and associated GM Hospital, Rewa, Madhya Pradesh during the period of 1st August 2015 to 31st July 2016, after clearance from the Institutional Ethics Committee. The study design is observational cohort study. The study group comprised of 100 consecutive children with cerebral malaria between age 1 month to 18 years presenting with acute febrile encephalopathy and either peripheral smear or Rapid diagnostic test positive for malaria with Glasgow Coma Scale ≤10 with or without seizures. All cases were malaria positive. Children were managed as per standard guidelines for treatment of cerebral and non-cerebral malaria. All cases were evaluated by ophthalmologist for any changes of retinopathy.

A detailed clinical evaluation including history and examination was carried out for all study participants at the time of admission. A base line evaluation in the form of blood sugar estimation (glucose strip), complete blood counts, and blood culture were done at the time of admission in all children. By using aseptic precautions, finger prick sample of blood was collected to prepare thick and thin smears of blood on glass slides, and evaluated for presence of any malarial parasite under oil immersion, as per standard procedures. Rapid diagnostic test kits were also used for the diagnosis of malaria. (SD BIOLINE Malaria Ag Pf./Pan kit manufactured by Standard Diagnostics (Alere) limited, Korea.)

Fundus examination was performed by ophthalmologist in all patients, after pupils were fully dilated using mydriatic eye drops. Presence of papilledema, retinal haemorrhages and vessel changes, peripheral whitening, and blurring of disc margins were noted and recorded separately, in addition to any other ophthalmologic abnormality.

Subsequently, all investigations required for clinical management were done.

In unconscious patients, vitals, Glasgow Coma Score and blood sugar were recorded until they became conscious or till demise. Initially, it was done every 6 hours for first 24 hours then every 12 hours until they became conscious.

Statistical analysis: The data of the study were entered and analysed using the software Microsoft Excel 2013 for windows. Appropriate univariate and bivariate analysis 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 (χ²) test for categorical variables. The critical levels of significance of the results were considered at 5% i.e. P< 0.05 was considered significant.

Results
In our study in cerebral malaria (malaria positive with encephalopathy) 59% were males and 41% were female patients. (Table no. I)

In cerebral malaria out of 100 cases, 12 cases were Plasmodium vivax positive, 74 cases are Plasmodium falciparum positive, and 14 cases are
both Plasmodium vivax and Plasmodium falciparum positive. Out of total 41 cases of retinopathy maximum cases were Plasmodium falciparum positive (78%), Plasmodium vivax is positive in 2.5% of cases. While 19.5% cases were both pv and pf positive. (Table II)

| Table I: Sex | Cerebral malaria(CM) (n=100) |
|-------------|-----------------------------|
| Male (M)    | 59 (59%)                    |
| Female (F)  | 41 (41%)                    |
| Total       | 100 (100%)                  |

| Age          | Retinopathy (CM group) |
|--------------|------------------------|
|              | Total | Pv  | Pf  | Both |
| <6 month     | 41    | 1 (2.5%) | 32 (78%) | 8 (19.5%) |
| 6 month – 5 years | 59    | 11 (19%) | 44 (71%) | 12 (20%) |
| 6 years – 12 years | 27    | 74   | 6 (10%) |
| 13 years – 18 years | 47    | 14   |

**Table II: Incidence of retinopathy in relation to *Plasmodium* species in Cerebral malaria**

| Retinopathy (CM group) | Total | Pv | Pf | Both |
|------------------------|-------|----|----|------|
| Present                | 41    | 1  | 32 | 8    |
| Absent                 | 59    | 11 | 42 | 14   |
| Total                  | 100   | 12 | 74 | 14   |

**P value** 0.0309

**Discussion**
In our study we found that in the Cerebral malaria (malaria positive with encephalopathy) 59% patients had normal fundus and 41% patients had retinopathy. In cerebral malaria, 74% were infected with isolated Plasmodium falciparum and 12% cases with isolated plasmodium vivax, while 14% were infected with both the species. Thus Plasmodium falciparum was the most common cause of cerebral malaria.

Jain, et al. had also reported 96% cases of cerebral malaria caused by Plasmodium falciparum in their study[^12]. In our study we also found cases of cerebral malaria which were caused by plasmodium vivax which was in accordance with the observation of Ahmed[^13] and Gopinathan[^14].

Retinopathy was seen more frequently with Plasmodium falciparum (78%) compared to P vivax (2.5%). The difference in the incidence of retinopathy in P.falciparum cases and P vivax cases in both groups was statistically significant (p<0.0309). Thus showing retinopathy was significantly correlated with P.falciparum malaria.

**Conclusions**
Plasmodium falciparum was the most common cause of cerebral malaria in the study but we also found cases of cerebral malaria which were caused by plasmodium vivax and some of the cases which were infected with both species together.

Malarial retinopathy is significantly associated with P.falciparum species of malarial parasite in children with cerebral malaria indicating P.falciparum as the most important cause of cerebral malaria or serious disease.

**References**
1. Koram KA, Molyneux ME. When is “Malaria” malaria? The different burdens of malaria infection, malaria disease, and malaria-like illnesses. *Am J Trop Med Hyg* 2007; 77:1-5.
2. Snow RW, Guerra CA, Noor AM, Myint HY, Hay. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature 2005 434 214-217.
3. White VA, Lewallen S, Beare N, Kayira K, Carr RA, Taylor TE. Correlation of retinal aemorrhages with brain haemorrhages in children dying of cerebral malaria in Malawi. *Trans R Soc Trop Med Hyg* 2001;95: 618–621.
4. Snow RW, Newton CRJC, Craig MH & Steketee RW. The public health burden of plasmodium falciparum malaria in Africa: deriving the numbers. Disease Control Priorities Project Working 2003, Paper No. 11. Bethesda, Md.
5. Mac Pherson GG, Warrell MJ, White NJ, Looareesuwan S, Warrell DA. Human cerebral malaria. A quantitative ultrastructural analysis of parasitized erythrocyte sequestration. Am J Pathol 1985; 119:385–401.

6. Pongponratn E, Riganti M, Punpoowong B, Aikawa M. Microvascular sequestration of parasitized erythrocytes in human falciparum malaria: a pathological study. Am J Trop Med Hyg 1991; 44:168–75.

7. Silamut K, Phu NH, Whitty C, et al. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. Am J Pathol 1999; 155:395–403.

8. Pongponratn E, Turner GD, Day NP, et al. An ultrastructural study of the brain in fatal Plasmodium falciparum malaria. Am J Trop Med Hyg 2003; 69:345–59.

9. Taylor TE, Fu WJ, Carr RA, et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. Nat Med 2004; 10: 143–5

10. Jain V, Avinash C, Pradeep K, Mannmohan S, Mrigendra P, Rasik B, et al. Burden of cerebral malaria in Central India (2004–2007). Am J Trop Med Hyg. 2008;79:636

11. 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;51:2858.

12. Beare NAV, Southern C, Kayira K, Taylor TE, Harding SP. Visual outcomes in children in Malawi following retinopathy of severe malaria. Br J Ophthalmol 2004 88 321-324.

13. Birbeck G, Beare N, Lewallen S, Glover SJ, Molynieux ME, Kaplan PW & Taylor TE. Identification of malaria retinopathy improves the specificity of the clinical diagnosis of cerebral malaria: findings from cohort study. 2010a, Am J Trop Med Hyg, 2010 82. 231-4.

14. Kuchar & Shubhakaran, et al. Ophthalmologic abnormalities in adults with plasmodium falciparum malaria; Q J Med. 1998., 91:845-852.

15. Jain Vidhan, Avinash C, Pradeep K, Mannmohan S, Mrigendra P, Rasik B, Aditya P, Saroj K, Venkatachalam U, Jonathan K, And N Singh; Burden of cerebral malaria in central India (2004–2007). Am J Trop Med Hyg. 2008 October; 79(4): 636–642

16. Ahmed SH, Moonis R, Kidwai T; Cerebral malaria in children, Indian Journal Pediatr. 1986. 53:409-413,

17. Gopinathan VP, Ratla PK, Bhoptc AG; Falciparum malaria in North Eastern Sector; JAPI Ind. Vol29, Dec. 1981.

18. Koram KA, Molyneux ME. When is “Malaria” malaria? The different burdens of malaria infection, malaria disease, and malaria-like illnesses. Am J Trop Med Hyg2007 77 1-5.

19. Snow RW, Guerra CA, Noor AM, Myint HY, Hay. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature 2005 434 214-217.

20. White VA, Lewallen S, Beare N, Kayira K, Carr RA, Taylor TE. Correlation of retinal aemorrhages with brain haemorrhages in children dying of cerebral malaria in Malawi. Trans R Soc Trop Med Hyg 2001;95: 618–621.