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A Hospital-Based Retrospective Comparative Study of Complications, Outcomes, Clinical and Laboratory Parameters of Malaria with and without Neurological Involvement

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Abstract. ***Background & Objectives:*** **Classically associated with *Plasmodium (P.) falciparum*, neurological complications in severe malaria is associated with increased morbidity and mortality. However, reports implicate the long considered benign *P. vivax* for causing severe malaria as well. We aimed to analyse the cerebral complications in malaria, and study if there is a species-related difference in the presentation and outcomes.**

Methods: **We retrospectively compared patients with malaria hospitalised from 2009-15, with (n=105) and without (n=1155) neurological involvement regarding outcomes, complications, demographic attributes, clinical features, and laboratory parameters. Subsequently, the same parameters were studied in those with cerebral malaria due to mono-infections of *P. vivax* or *P. falciparum* and their co-infection.**

Results: **Cerebral malaria was observed in 8.3% (58/696), 7.4% (38/513) and 17.6% (6/51) of *P. vivax*, *P. falciparum* and combined plasmodial infections respectively. Those with cerebral malaria had significantly ($p<0.05$) longer hospitalisation, delayed defervescence, required mechanical ventilatory support and dialysis despite comparable levels of azotemia and renal insufficiency, and adverse outcomes compared to non-cerebral malaria. Severe thrombocytopenia, respiratory distress and mechanical ventilation were significantly ($p<0.05$) associated with *P. vivax* cerebral malaria.**

Conclusions: **The plasmodial species are comparable in clinical and laboratory parameters and outcomes in cerebral malaria in isolation and combination ($p>0.05$). *P. vivax* is emerging as the predominant cause of cerebral malaria, and its virulence is comparable to *P. falciparum*.**

Keywords: acute malaria, cerebral malaria, malaria outcome, *P. falciparum*, *P. vivax.*

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Introduction. Cerebral involvement is a severe manifestation of acute malaria. In endemic countries, the central neurological system is more frequently and more severely affected regarding sequelae in children than in adults, presumably, because adults acquire some degree of immunity with age after repeated episodes of malarial infection.[1] Cerebral malaria is a multifactorial disease- seizures, impaired substrate delivery leading to hypoxia and hypoglycaemia, reduced perfusion due to shock, hypovolemia and acidosis are the proposed pathogenetic mechanisms. Cytoadhesion of parasitized red blood cells to the brain microvessels seems to be the main histopathological finding; immunological factors (leukocytes, cytokines and chemokines), platelets, nitric oxide scavengers and heme, are additionally involved in the development of the disease. These factors integrate a systemic inflammatory response during a malarial infection that acts in the brain and is largely responsible for the clinical features pertaining to the nervous system. However, it is not known to what extent and timing each factor contributes to the pathogenesis and interferes with the prognosis of the disease.[2]

Neurological sequelae may develop in 5-11% cases with cerebral malaria, and a fraction of patients may suffer long-term neurological impairments.[3,4,5,6] While the mortality attributed to malaria in India[7] is 0.05%, the figure multiplies manifold in those with cerebral involvement. Mortality in cerebral malaria was reported as 5.5-7% in children in Africa[3,8] and 20% in adults in South Asia.[9] Concomitant acute renal failure and metabolic acidosis cause a 6-fold increase in mortality suggesting associated vital organ dysfunction has a summative effect on mortality in severe malaria.[10] Nearly 75% of deaths in children and 20% mortality in adults with cerebral malaria occurs within the first 24 hours before they can benefit from the full effect of antimalarials.[1] Lactic acidosis, severe anaemia, hypoglycaemia, retinal haemorrhages and leucocytosis have been proven to be associated with mortality and the development of neurological sequelae in some studies..[10,11]

The major thrust for reducing mortality and morbidity is on vector control and development of the yet elusive effective vaccine. Nevertheless, recognition of the early signs of neurological involvement and indicators of poor outcome can allow the prompt initiation of the available therapies for the malarial infection. Although, artemisinin combination therapy (ACT) is recommended and the drugs are freely available and used in the urban areas, older drugs like chloroquine and quinine are the cornerstone of treatment in the countryside given their availability in the national malaria control programme. Infection with chloroquine-resistant organisms and delay in initiation of ACT may also account for complications, sequelae and increased mortality.

Myriad presentations of acute malaria due to *P. vivax* and *P. falciparum* in isolation as well as in combination have been regularly observed in this part of the world.[12] Though traditionally attributed to *Plasmodium (P.) falciparum* infection, the cerebral manifestations are increasingly being recognised in those infected with *P. vivax.* We hypothesised that cerebral malaria due to different etiological species is different in term of presentation, complications and outcomes. We undertook this study to test our hypothesis and also to compare the outcomes and complications in cerebral and non-cerebral malaria. We also intended to identify the demographic attributes, clinical features, and haematological and biochemical parameters precluding cerebral involvement.

Materials and Methods.

Study setting: Uttarakhand is a hilly north Indian state with the Ganges being the major river system. It is surrounded by Tibet in the north, Nepal to the east and the Indian states of Uttar Pradesh and Himachal Pradesh in the south and north-west respectively. The vegetation includes alpine meadows, subalpine conifer and subtropical pine forests, moist deciduous forests and grasslands. Nearly 70% of its 10 million population resides in rural areas. Uttarakhand has two principal divisions – Garhwal and Kumaon comprising of seven and six districts respectively. The Himalayan Hospital is a 1000 bed tertiary care teaching hospital affiliated with the Himalayan Institute of Medical Sciences located 25 km from Dehradun, the capital of Uttarakhand. The hospital caters mainly to the Garhwal division, some districts of the Kumaon division and the densely populated adjoining districts of Uttar Pradesh.

Patient Selection: Ours was a retrospective hospital-based observational study approved by the institutional research and ethics committees of the Swami Rama Himalayan University. All patients hospitalised for acute malaria over a period of 6 years (2009-2015) were included in the study. The diagnosis of acute malaria was considered if the peripheral blood smear was positive and the included subjects were categorised as having malaria due to *P. falciparum, P. vivax* or both the species.

Data Collection: Clinical information including the duration of fever, associated symptoms (nausea, vomiting, headache, loose stools, breathlessness, abdominal pain, bleeding manifestations and the site of bleed, if present, seizures, unconsciousness, oliguria and swelling over the body, etc) and signs (heart rate, blood pressure, respiratory rate, oxygen saturation, palpable organomegaly and other abnormal clinical findings) at the time of presentation in the hospital was retrieved from the hospital records for all patients included in the study. Demographic details including age, gender and occupation were also collected and compiled. The haematological and biochemical investigations carried out at the time of hospitalisation were also noted. Outcomes studied were mortality and morbidity (the duration of hospitalisation, hypoglycemic events, shock, bleeding, severe thrombocytopenia, organ dysfunction, time to regain consciousness and defervescence, time to recovery of platelets and creatinine, and the need for transfusion, intensive care, mechanical ventilation and dialysis).

Severe malaria was diagnosed as per the WHO guidelines issued in 2012 and 2015 with minor modifications in a bid to define organ dysfunction. Cerebral malaria was diagnosed if more than two episodes of convulsions were reported in 24 hours or the subject was disoriented at presentation (A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children) in the absence of other biochemical abnormalities precluding neurological dysfunction. Renal impairment was defined as a rise in blood urea nitrogen (BUN) > 20 mmol/l and serum creatinine (> 3 mg/dl). Pulmonary involvement (respiratory distress) was defined as tachypnea (>30/min) along with a fall in oxygen saturation to <92%. Liver dysfunction was defined as a two-fold rise in alanine transaminases [Normal value: 10–40 IU/l]; isolated hyperbilirubinemia i.e. (1.5-6 mg/dl) was not attributed to liver dysfunction if liver transaminases were within normal limits. The definition of jaundice followed by us is different from that by the WHO as the parasite count mandated by the latter was not available in most of our patients. The increase in platelet count in consecutive samples, or beyond 50,000/mm^3 when less at presentation was considered as recovery of platelet counts.[12] Improvement in serum creatinine was taken into account when elevated serum creatinine normalised to lie within the reference range.

Data Analysis: Data was analysed using the statistical software SPSS version 22. Qualitative data was presented in the form of frequency and percentage, and quantitative data as a mean $\pm$ standard deviation. It was observed that the data was not normally distributed; the Kruskal-Wallis – H test was used to compare the difference among groups followed by Mann-Whitney U test to compute the differences between the groups. Chi-square and Fisher's exact tests were used to check the significance of the differences in categorical variables. A $p < 0.05$ was considered as statistically significant.

Results. A total of 1649 patients (age range: 2 months to 96 years) of acute malaria were treated at our centre over the last six years. Of these, 389 patients were excluded due to inadequate clinical, haematological and biochemical data and/or the analysis was performed on 1260 patients. Of those included, 63.1% hailed from rural areas. The average delay in seeking specialized care was 6.3 days; qualified as well as unqualified medical personnel treated 82.2% (n=1306) patients in the periphery. Treatment was with chloroquine in 79.1%, artemisinin compounds in 15.0% and 5.7% with quinine; duration and doses prior to the presentation were variable. The patients aged less than 18 years accounted for 25% of all cases and were treated by the paediatricians. A little over half of the patients were infected with *P. vivax* (n= 696; 55.2%), 513 (40.7%) with *P. falciparum* and 51 (4.0%) with both the plasmodial species. Overall, 96.5% of all patients were febrile at presentation with chills and rigours reported by 74.7% patients. Nausea and/or vomiting and headache were reported in 45.7% and 26.1% patients respectively. Giddiness and hiccoughs

were experienced by 2.5% and 0.8%. The overall mortality (and loss to follow-up taken together) was 4.9%.

Neurological manifestations were observed in 8.3% (58/696), 7.4% (38/513) and 17.6% (9/51) of *P. vivax, P. falciparum* and mixed plasmodial infections respectively. Of all the patients with cerebral malaria (n=105), 40.9% were less than 18 years of age. Seizures were observed in 25 (40.3%) and 28 (65.1%) adults and children respectively while the remaining presented with unconsciousness without overt seizure activity. Symmetrical upper motor neurone signs including increased muscle tone and brisk tendon reflexes were observed in 76.1% cases with patellar and/or ankle clonus (20%), and extensor plantar responses (70.4%). Abdominal reflexes were universally absent wherever documented. Reduced oral intake and restlessness were observed in 3 patients each (2.8%) in the paediatric age group. Restlessness and paraesthesias were noticed before unconsciousness in 3 (4.8%), opsoclonus in 1 while focal weakness was observed in 3 adult patients.

Table 1 shows the comparative analysis of patients with and without neurological manifestations regarding demographic, clinical, haematological and biochemical parameters, complications and the outcomes. Those with cerebral malaria were younger in age with a greater likelihood of presenting with enlargement of the spleen and/or the liver, a low haemoglobin and serum albumin in comparison to those without neurological manifestations. These patients defervesce significantly later, had a significantly greater hospital stay, more blood transfusions, and greater need for hemodialysis and mechanical ventilation as compared to their counterparts without cerebral malaria. Also, their comparative chances of deteriorating while on treatment and succumbing to the disease 12.3% vs. 4.2%; p< 0.001) were significantly more. Of the 13 patients who succumbed, one had pure cerebral involvement. Four mortalities occurred in children < 5 years of age while one adolescent (15 years) died. ACT was used to treat the patients in 95.1% (1199/1260); non-clearance of the parasite from the blood smears and/or non-resolution of fever within three days of proper therapy led to its replacement with quinine in 6 (0.5%) cases. Quinine was used as the initial treatment in 61 (4.8%) cases.

Table 1. Comparison of demographic, clinical, haematological and biochemical parameters, complications and outcomes of acute malaria with and without neurological involvement.

Parameters	**Cerebral Malaria**		**p-value**
	Yes [105]	**No [1155]**	
Demography			
Age (years)	28.8 ± 20.4 [104]	31.9 ± 17.4 [1153]	0.016
Sex (M/F)	64.8/35.2	61.5/ 38.5	0.290
Rural/Urban	69.5/ 30.5	62.6/ 37.2	0.095
P. vivax	55.2	55.2	0.041
P. falciparum	36.2	41.1	
Both	8.6	3.6	
Duration of fever (days)	6.3 ± 3.8 [105]	6.4 ± 3.9 [1155]	0.936
Symptoms			
Fever	96.2	96.5	0.507
Chills/ rigors	74.3	74.8	0.494
Nausea/ vomiting	46.7	45.7	0.465
Headache	29.3	25.8	0.235
Jaundice	21.9	16.1	0.085
Breathlessness	8.6	8.5	0.544
Bodyache	13.3	22.3	0.019
Loss of appetite	8.9	15.1	0.042
Bleeding	19.0	16.5	0.286
Abdominal pain	21.0	28.4	0.062
Pedal edema	0.9	2.0	0.392
Loose motions	8.6	7.3	0.369
Oliguria	7.6	3.6	0.050
Malaise	6.7	7.2	0.519
Cough	4.8	7.4	0.210
Burning in micturition	1.9	2.9	0.410

Signs			
Shock	29.5	22.2	0.058
Pallor	43.8	26.2	<0.001
Splenomegaly	36.2	25.1	0.011
Hepatomegaly	51.4	34.4	<0.001
Lab Investigations			
Oxygen saturation (%)	96.3 ± 4.8 [53]	96.8 ± 4.9 [543]	0.778
Hemoglobin (gm/dl)	8.8 ± 2.9 [102]	10.5 ± 14.3 [1137]	<0.001
TLC (x 10^3/ cumm)	9.7 ± 7.2 [102]	6.3 ± 4.3 [1135]	<0.001
Polymorphonuclear cells (%)	63.7 ± 16.0 [97]	62.6 ± 15.0 [1037]	0.411
Lymphocytes (%)	29.3 ± 15.4 [97]	29.4 ± 14.3 [1036]	0.616
Monocytes (%)	5.6 ± 4.3 [96]	5.9 ± 4.8 [1033]	0.635
Eosinophils (%)	1.7 ± 2.1 [91]	1.7 ± 2.2 [957]	0.833
Mean corpuscular volume (fl)	84.6 ± 9.6 [94]	86.7 ± 36.4 [1056]	0.202
Mean corpuscular haemoglobin	27.8 ± 4.0 [94]	28.4 ± 3.9 [1055]	0.162
MCH concentration (%)	32.8 ± 2.1 [94]	33.3 ± 9.4 [1051]	0.448
Platelet count (x 10^3/cumm)	85.9 ± 94.4 [101]	63.0 ± 74.2 [1133]	0.050
ESR (/1^{st} hour)	51.2 ± 24.9 [36]	52.2 ± 29.0 [482]	0.950
Actual bicarbonate (mg/dl)	16.6 ± 5.0 [8]	16.9 ± 4.8 [74]	0.963
Creatinine phosphokinase	588.5 ± 666.5 [6]	72.2 ± 129.9 [31]	<0.001
Alanine transaminase (IU/l)	55.2 ± 47.6 [74]	50.0 ± 66.2 [904]	0.097
Aspartate transaminase (IU/l)	101.1 ± 112.7 [69]	80.9 ± 210.8 [870]	0.001
Alkaline phosphatase (IU/l)	118.6 ± 66.5 [47]	120.8± 81.8 [584]	0.855
Lactate dehydrogenase (IU/l)	1222.7 ± 908.7 [11]	748.0 ± 836.4 [63]	0.036
Serum bilirubin (mg/dl)	5.5 ± 6.9 [59]	3.3 ± 4.3 [857]	0.270
Total serum protein (g/l)	5.7 ± 1.0 [41]	5.7 ± 0.8 [534]	0.178
Serum albumin (g/l)	2.3 ± 0.7 [46]	2.5 ± 0.6 [613]	0.038
Blood urea nitrogen (mmol/l)	58.9 ± 53.3 [60]	28.3 ± 28.9 [789]	<0.001
Serum creatinine (mg/dl)	2.0 ± 2.4 [92]	1.5 ± 2.0 [1013]	0.775
Serum sodium (mmol/l)	137.3 ± 7.2 [90]	135.6 ± 5.4 [939]	0.025
Serum potassium (mmol/l)	4.4 ± 0.8 [88]	4.1 ± 1.7 [934]	<0.001
Complications & Outcomes			
Hypoglycaemia	14.2	10.2	0.187
Defervescence	3.3 ± 3.0 [63]	2.3 ± 1.7 [555]	0.015
Duration of hospitalization (days)	7.1 ± 4.0 [105]	5.1 ± 2.5 [1064]	<0.001
Anemia	72.8	74.2	0.418
Blood transfusion	32.4	16.3	<0.001
Liver dysfunction	21.0	17.1	0.189
Respiratory failure	16.1	4.3	<0.001
Mechanical ventilation	10.5	1.8	<0.001
Severe Thrombocytopenia (<20 x 10^3/cumm)	27.6	30.9	0.509
Platelet transfusion	24.8	23.4	0.414
Improvement in platelet counts (days)	3.2 ± 1.8 [34/51]	2.5 ± 1.7 [456/710]	0.017
Renal failure	25.7	19.3	0.077
Improvement in azotemia (days)	4.9 ± 2.5 [7/27]	3.9 ± 3.5 [58/223]	0.179
Haemodialysis	12.4	3.0	<0.001
Organ dysfunction	0.2 ± 0.5 [99]	0.2 ± 0.4 [1143]	0.643
Improved/Expired	87.6/ 12.4	95.8/ 4.4	0.001

Figures in parenthesis indicate the number of cases where information was available. Continuous data is expressed as Mean ± S.D; categorical variables as percentage of total of columns.

In the second step, we compared the complications and outcomes in patients with cerebral malaria based on the etiological species. Jaundice was reported significantly more in falciparum cerebral malaria than the other subgroups. However, no significant difference in the etiological groups in terms of clinical, haematological and biochemical characteristics barring a couple of red cell parameters (mean corpuscular haemoglobin and its concentration) was observed. The associated complications and outcome measures are shown in **Table 2**. Respiratory distress and failure requiring mechanical ventilation and/or intensive care were

Table 2. Comparison of complications and outcomes of cerebral malaria due to different species.

Parameters	P. vivax (n=58)	P. falciparum (n=38)	Both (n=9)	p-value
Hypoglycaemia	8.6	15.7	44.4	0.015
Defervescence	2.8 ± 2.9 [42]	4.7 ± 3.4 [16]	2.4 ± 2.1	0.090
Consciousness regained (days)	2.2 ± 1.0 [58]	2.3 ± 0.9 [38]	1.8 ± 1.3 [9]	0.418
Duration of hospitalization (days)	7.2 ± 4.1 [58]	7.2 ± 3.9 [38]	6.2 ± 4.1 [9]	0.794
Shock	27.6	34.2	22.2	0.692
Anemia	83.6	86.8	77.8	0.781
Blood transfusion	31.0	28.9	55.6	0.292
Liver dysfunction	31.0	23.7	11.1	0.545
Respiratory failure	15.5	2.6	26.6	0.003
Mechanical ventilation	13.8	0.0	33.3	0.006
Severe Thrombocytopenia (<20 x 10^3/cumm)	32.7	26.3	0	0.120
Platelet transfusion	37.9	7.9	11.1	0.002
Improvement in platelet counts (days)	3.2 ± 1.7 [21]	3.2 ± 2.0 [12]	2 [1]	0.801
Renal failure	25.9	28.9	11.1	0.545
Improvement in azotemia (days)	4.4 ± 2.9 [5/15]	6.0 ± 1.4.5 [2/11]	-	0.503
Haemodialysis	8.6	18.4	11.1	0.359
Organ dysfunction	0.2 ± 0.4 [58]	0.3 ± 0.7 [38]	0.4 ± 0.7 [9]	0.164
Expired	10.3	10.5	33.3	0.136

Figures in parenthesis indicate the number of cases where information was available. Continuous data is expressed as Mean ± S.D; categorical variables as percentage of total of columns.

not observed in *P. falciparum* mono-infections; however, the requirement rose significantly with *P. vivax* co-infection (p=0.003). Two patients infected with both the *Plasmodial spp.* had manifest bleeding of which 1 received platelet transfusion despite having mild thrombocytopenia (1.0-1.5 lacs/cumm). Anaemia was universally seen across the three etiological groups with no significant difference between the haemoglobin and hematocrit values. The mean serum creatinine values (mg/dl) were 1.9, 2.2 and 1.7 (p>0.05) for *P. vivax, P. falciparum* and co-infection groups respectively.

Of the 13 patients who succumbed, shock (n=31), anemia (n=86), renal dysfunction (n=27), liver dysfunction (n=28), respiratory failure (n=14) were associated in 5, 11, 7, 5 and 3 patients respectively; more than 2 complications were observed in 9 patients. Mortality in cerebral malaria was significantly associated with concomitant renal insufficiency (p=0.020); association with shock, anaemia, respiratory failure and liver dysfunction was not significant (p>0.05).

Discussion. In the present study, greater morbidity and higher mortality were observed in acute malaria patients with neurological complications. However, cerebral malaria due to *P. vivax* or *P. falciparum* in isolation or combination did not apparently differ significantly in terms of morbidity and mortality. The predictive value of development of cerebral complications is poor with regard to demographic, clinical and laboratory parameters. Cerebral manifestations developed in 13.6% of all children and adolescents, and 6.5% of all adults with malaria. The higher incidence in children is consistent with the existing literature and is apparently due to inadequate immune response to the endemic infection. Another prominent observation is that *P. vivax* has overtaken *P. falciparum* as the predominant species producing neurological manifestations over the years in term of the number of cases although the association is not statistically significant (p=0.596).

The neurological symptoms and signs elicited at the time of presentation are similar in frequency to that described in the literature.[1,9] Earlier studies suggested that surviving patients fully recover,[13] but publications over the past 20 years highlight that many children sustain a significant brain injury. Nearly 11% are discharged with gross neurological deficits[4,5] though some deficits such as blindness, ataxia, and central hypotonia improve with time.[6] Almost a quarter of these have long-term impairments about cognition, motor function, or behaviour while epilepsy develops in 10%.[6,14,15,16] The main risk factors for neurological sequelae identified include repeated

seizures, profound and prolonged coma, intracranial hypertension, and hypoglycemia.[17] None of our patients suffered neurological sequel apparently due to the absence of the risk mentioned above factors. Hypoglycemia (plasma glucose < 40 mg/dl) occurs in about 8% of adults[18] and about 20% of children with cerebral malaria.[19] In our study, hypoglycemia was documented in 14.2% cases of cerebral malaria.

The incidence of seizures in adults has been variably described as 10-50% in studies from South Asia;[1,9,20] seizures were reported in 40% adults with cerebral malaria in our study. Differences in the parasite virulence characteristics and the decreased use of chloroquine pretreatment may account for this wide variation in the incidence of seizures. Also, the seizures are partial motor and occasionally subtle (especially in children) such as repetitive eye or hand movements and occult. Although more than one seizure is frequent, status epilepticus is unusual in adults, and consciousness after a seizure is usually obtunded.[9,10] Given the facts mentioned above, the fraction of seizures observed in our study is apparently an underestimation.

Clinical features, namely anorexia and body ache, were reported significantly more from those with intact consciousness for obvious reason. Hepatosplenomegaly and pallor observed significantly more in those with cerebral malaria were presumably associated with increased hemolysis suggested by significantly higher ($p<0.05$) aspartate transaminase and lactate dehydrogenase levels translated into significantly lower haemoglobin and higher rates of transfusion ($p<0.05$). The morbidity was significantly more ($p<0.05$) in those with cerebral compared to those without non-cerebral malaria apparently due to delayed defervescence, need for assisted mechanical ventilation, dialytic support and transfusions.

Although bleeding manifestations and mean haemoglobin and hematocrit levels were comparable amongst the etiological groups, significantly more patients with vivax cerebral malaria received platelet transfusions. This occurs mainly because of the severe thrombocytopenia detected in nearly a third of all with *vivax* cerebral malaria. Similarly, respiratory distress and incumbent mechanical ventilation were significantly more ($p<0.05$) in *vivax* cerebral malaria. Moreover, the incidence of renal and liver dysfunction, occurrence of anaemia and shock, organ dysfunction and mortality in those with cerebral malaria due to *P. vivax* was comparable to *P. falciparum*. These data imply the exponential rise of the malignant potential of *P. vivax* given the increasing fraction of *P. vivax* as the cause of severe malaria. Although, the lower numbers in co-infected etiological group desist us from drawing any conclusion, evidence from existing literature lends credence to our observation of the protective effect of co-infection of *P. vivax* and *P. falciparum*[21] at least for severe thrombocytopenia and renal failure, though it does not extrapolate to the other organs and mortality. The reason for this disparity may be related to which plasmodial species pre-existed and which superinfected. *P. vivax* superinfection over an existing *P. falciparum* infection raises *P. falciparum* parasitaemia thereby causing severe malaria. In contrast, *P. falciparum* superinfection over an existing *P. vivax* infection reduces *P. falciparum* parasitaemia and hence, protecting from the development of severe malaria.[21]

The overall mortality of adult cerebral malaria is about 20% (10); 12.9% (n=8) of our adults with cerebral malaria died. Mortality depends on the associated vital organ dysfunction and rises from 8% in "pure" cerebral malaria to 50% with associated acute renal failure and metabolic acidosis.[10] An adverse outcome was significantly related to renal dysfunction and metabolic acidosis in our study too ($p<0.02$). One patient with concomitant respiratory compromise succumbed in our study. Mortality may also occur for want of intensive care facilities, renal replacement therapy and good nursing care. Most deaths (61.5%) occurred within 24 hours of hospitalization as was seen in earlier studies. Consciousness was regained in our study after a median of 2 days (2.2 ± 1.0 days) and the maximum duration was recorded as 5 days. As per the existing literature, those with a Glasgow coma score <11 needed a median of 2 days to regain consciousness but occasional adult patients may take more than 1 week.[10] In contrast to earlier studies,[3,11] hypoglycemia, deep coma, respiratory distress, circulatory failure, and heavy parasitemia in cerebral malaria were not found to be associated with mortality in the present study presumably due to availability of intensive and supportive management supplemented by good nursing care.

The limitations of our study are mainly its retrospective nature and its attendant biases, mainly reliance on hospital records that were incomplete at times. Neither, the level of parasitaemia was assessed routinely nor sequential peripheral blood smears were performed as a standard protocol. Due to this, we could not calculate the effect of parasitaemia on the complications and the outcome. Also, the defervescence could not be correlated to the disappearance of parasite from the peripheral smear. The effect of adequacy of treatment received prior to hospitalization and delay in the diagnosis was not taken into account. Also, PCR was not used to confirm the Plasmodial specie. Nevertheless, our reliance on objective parameters and inclusion of only those cases with adequate clinical, hematological and / or biochemical data circumvents this to a large extent. This is the first study with such a large number of patients of malaria from this part of the world to the best of our knowledge. Also, PCR is not available routinely for assessment of the species. Blood smear examination with trained pathologists is reliable, quite apparent from the low level of morbidity in our study. Prospective interventional studies evaluating the treatment practices and adequacy of treatment delivered are needed to understand the lacunae and improving the outcomes of cerebral malaria.

Conclusions. Neurological complications in malaria, classically caused in *P. falciparum* infections are increasingly being observed in *P. vivax* infections. The situation is alarming with *vivax* constituting the major burden of malaria in north India, little recognition of its malignant potential compounded by the almost comparable complications and outcomes. Our study may also prove to be an initiator for further research into possible genetic alterations that the parasite or its carrier may have incurred due to decades of insecticide use, injudicious use of conventional antimalarials, industrialization and ecological transformations and/ or possible co-infection with unrecognized viruses.

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