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 malaria infection. 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.

Neurological sequelae may develop in 5-11% cases with cerebral malaria, and a fraction of patients may suffer long-term neurological impairments. While the mortality attributed to malaria in India 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 and 20% in adults in South Asia. 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. 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. 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.

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. 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. 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 ± 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 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 plasmodal 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 hicchoughs...
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 |
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

| Signs          | Shock | Pallor | Splenomegaly | Hepatomegaly |
|----------------|-------|--------|--------------|--------------|
|                | 29.5  | 43.8   | 36.2         | 51.4         |
|                | 22.2  | 26.2   | 25.1         | 34.4         |
|                |       |        |              | <0.001       |
|                |       |        | 0.011        |              |
|                |       |        |               | <0.001       |

**Lab Investigations**

| Parameter                               | Mean ± S.D.       | Mean ± S.D.       | Mean ± S.D.       | Mean ± S.D.       |
|-----------------------------------------|-------------------|-------------------|-------------------|-------------------|
| 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 10⁷ /cumum)                      | 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 10⁷/cumm)             | 85.9 ± 94.4 [101] | 63.0 ± 74.2 [1133]| 0.050             |                   |
| ESR (/l 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]    | 3.5 ± 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**

| Complication                        | No. | %     | No. | %     | No. | %     |
|-------------------------------------|-----|-------|-----|-------|-----|-------|
| Hypoglycaemia                       | 14.2| 0.446 | 10.2| 0.28  |
| 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| 19.16 | 74.2| 19.52 |
| 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 10⁷/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.
The association is not significantly due to P. vivax or 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.\textsuperscript{13} Earlier studies suggested that surviving patients fully recover,\textsuperscript{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\textsuperscript{4,5} though some deficits such as blindness, ataxia, and central hypotonia improve with time.\textsuperscript{6} Almost a quarter of these have long-term impairments about cognition, motor function, or behaviour while epilepsy develops in 10%.\textsuperscript{6,14,15,16} The main risk factors for neurological sequelae identified include repeated...
seizures, profound and prolonged coma, intracranial hypertension, and hypoglycemia. 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 and about 20% of children with cerebral malaria. 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; 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. 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 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.

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. 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. In contrast to earlier studies, 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 intervention trials 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. 

References:

1. Idro R, Jenkins NE, Newton CRJC. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. Lancet Neurol 2005; 4: 827-40. https://doi.org/10.1016/S1474-4422(05)70204-7
2. Martins CY, Carvalho LMJ, Daniel-Ribeiro CT. Challenges in the Determination of Early Predictors of Cerebral Malaria: Lessons from the Human Disease and the Experimental Murine Models. Neuroimmunomodulation 2009; 16:134-145
3. Idro R, Karamagi C, Tumwine J. Immediate outcome and prognostic factors for cerebral malaria among children admitted to Mulago Hospital, Uganda. Annals Trop Paedia 2004; 24: 17-24. https://doi.org/10.1179/02724930425013240
4. Newton CR, Krishna S. Severe falciparum malaria in children: current understanding of pathophysiology and supportive treatment. Pharmacol Ther 1998; 79:1-53 https://doi.org/10.1016/S0163-7258(98)00008-4
5. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. Lancet 1990; 336:1039-43 https://doi.org/10.1016/S0140-6736(00)29498-7
6. van Hensbroek MB, Palmer A, Jaffar S, Schneider G, Kwiatkowski D. Residual neuralologic sequelae after childhood cerebral malaria. J Pediatr 1997; 131:125-129 https://doi.org/10.1016/S0022-3476(97)70135-5
7. http://hivbdcp.gov.in/malaria3.html [accessed on 22.04.2016]
8. Oluyuyemire OL, Brown BJ, Oyedeji OA, Adegoke SA, Adebamiro OJ, Oyedeyi GA. Clinical and laboratory predictors of outcome in cerebral malaria in suburban Nigeria. J Infect Dev Ctries 2007; 7 (8): 600-7.
9. Sattar MA, Hoque HW, Amin MR, Faiz MA, Rahman MR. Neurolological findings and outcome in adult cerebral malaria. Bangladesh Med Res Conc Bull 2009; 35: 15-17 https://doi.org/10.3329/bmrc.v35i1.2313 PMid:19637540
10. Newton CRJC, Hien TT, White N. Cerebral malaria. J Neurol Neurosurg Psychiatry 2000 69: 433-441. https://doi.org/10.1136/jnnp.69.4.433 PMid:10990900
11. Angyo IA, Pam SO, Szlachetka R. Clinical pattern and outcome in patients with acute severe falciparum malaria at Jos University Teaching Hospital, Nigeria. East Afr Med J 1996; 73:823-6. PMid:9103694
12. Saurabh Srivastava, Sohaib Ahmad, Nadia Shirazi, SK Verma, Prashant Puri. Retrospective analysis of vivax malaria patients presenting to tertiary referral centre of Uttarakhand. Acta Tropica 2011; 117: 82-85. https://doi.org/10.1016/j.actatropica.2010.10.001 PMid:20943199
13. Mantendam AH, Jaffar S, Bleichrodt N, van Hensbroek MB. Absence of neuropsychological sequelae following cerebral malaria in Gambian children. Trans R Soc Trop Med Hyg 1996; 90: 391-4 https://doi.org/10.1016/S0035-9203(96)00518-0
14. Ngoungou EB, Preux PM. Cerebral malaria and epilepsy. Epilepsia 2008; 49:19-24 https://doi.org/10.1111/j.1528-1360.2007.01752.x PMid:18754957
15. Carter JA, Mung’ala-Odera V, Neville BG, Muringa G, Mtoni N, Musumba C, Newton CR. Persistent neurocognitive impairments associated with severe falciparum malaria in Kenyan children. J Neurol Neurosurg Psychiatry 2005; 76:476-81 https://doi.org/10.1136/jnnp.2004.034893 PMid:15774431
16. John CC, Bangirana P, Byarugaba J, Opopka RO, Idro R, Jurek AM, Wu B, Boivin MJ. Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics 2008; 122:e92-e99 https://doi.org/10.1542/peds.2007-3709 PMid:18541616
17. PMid:2067241
18. Idro R, Mara K, John CC, Newton CRJ. Cerebral Malaria: Mechanisms of Brain Injury and Strategies for Improved Neurocognitive Outcome. Paediat Res 2000; 68 (4): 267-74. https://doi.org/10.1203/PDR.0b013e3181e7e78 PMid:20660660
18. PMid:3058312
19. White NJ, Warrell DA, Chanthavanchich P, et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. N Engl J Med 1989; 320:391-6. https://doi.org/10.1056/NEJM198910203201602 PMid:634877
20. Taylor TE, Molynieux ME, Wirima JJ, et al. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. N Engl J Med 1988;319:1040-7. https://doi.org/10.1056/NEJM198810203191602 PMid:3050516
21. Tripathy R, Parida S, Das L, Mishra DP, Tripathy D, Das MC, Chen H, Maguire JH, Panigraphi P. Clinical Manifestations and Predictors of Severe Malaria in Indian Children. Pediatrics 2007;
21. Mohapatra MK, Dash LK, Bartha PK, Karua PC: Profile of mixed species (Plasmodium vivax and falciparum) malaria in adults. J Assoc Physicians India. 2012, 60: 20-24. PMid:23777020