

Clinical profile of severe malaria: study from a tertiary care center in north India

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Abstract One hundred and sixty patients having clinical features of severe malaria reported during monsoon season–August–October 2010 at this tertiary care center of north India. Of these 110 (68.75 %) had *Plasmodium vivax* infection, 30 (18.75 %) were infected with *P. falciparum* and 20 (12.5 %) had co-infection due to *P. vivax* and *P. falciparum*. The diagnosis was made using Rapid Card Test and was confirmed by peripheral smear examination of thick and thin films. Several complications such as acute kidney injury, jaundice, severe anemia, metabolic acidosis, shock, hyperpyrexia, hypoglycemia, generalized tonic-clonic convulsions etc. were found to be more prevalent in patients with *P. vivax* infection. These symptoms were until recently known to be associated with falciparum malaria.

Keywords *Plasmodium vivax* · *Plasmodium falciparum* · Severe malaria · Co-infection

Introduction

The burden of malaria mortality is double than estimated in the World Malaria Report (2011). India is only second to Africa where the largest number of deaths occur due to malaria (Murray Christopher et al. 2012). Dhingra et al. (2010) estimated that about 200,000 people die of malaria in India each year. Until recently *Plasmodium falciparum* was considered to be the main cause of complicated malaria, but now severe clinical consequences resulting from vivax

malaria have been reported (Kochar et al. 2005; Diamond-Smith et al. 2009). In the recent years a large number of cases of complicated malaria caused by *Plasmodium vivax* have been reported. The objective of the present work is to highlight the prevalence of severe malaria caused by *P. vivax* and to emphasize the need to recognize the clinical symptoms and aggressively treat the patients to avert the consequent mortality. Although the presentation of these patients has been like those infected with *P. falciparum* but on investigation the causative agent found was *P. vivax*. What needs to be emphasized is the need to be watchful with such patients and to widen our sphere of differentials and consider that *P. vivax* can lead to severe malaria. Such patients if managed aggressively and treated accordingly can have a better outcome. In the present work an effort has been made to delineate the cause of various clinical manifestations of severe malaria, which until now were thought to be a hallmark of *falciparum* malaria.

Materials and methods

This is a single center, retrospective, observational study in which 160 patients admitted to a tertiary care center of western Uttar Pradesh from 1st August 2010 to 31st October 2010 with complaints of fever with chills and having clinical features of severe malaria were included. These patients were screened for a possible malaria infection using a Rapid Card Test and then confirmed by examination of thick and thin films in the peripheral smear by two different pathologists. Those patients not infected with *P. vivax* or *P. falciparum*, in whom IgM was positive for leptospira by ELISA, who were IgM and IgG positive for typhoid by ELISA and those who were IgM and IgG positive for dengue were excluded from the study.

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The cases found to be infected with *P. vivax*, *P. falciparum* or a co-infection were managed accordingly with artesunate based combination therapy, doxycycline and clindamycin. Patients with acute kidney injury (serum creatinine >3), jaundice (serum bilirubin >3 mg/dl), severe anemia (hemoglobin <5 g/dl), metabolic acidosis, shock, hyperpyrexia, hypoglycemia, generalized tonic-clonic convulsions were found out in each category (*P. vivax*, *P. falciparum* and co-infection). The percentage involvement in each category was calculated. Application of one-way ANOVA-*F* test showed a high-significant difference among different groups at 5 % level of significance (p value <0.05). Mean and standard deviation of variables in all the three categories were calculated.

Results

In the present pool of 160 patients, 110 (68.75 %) had *P. vivax*, 30 (18.75 %) had *P. falciparum* and 20 (12.5 %) had co-infection due to *P. vivax* and *P. falciparum*. The mean age of involvement of patients with *P. vivax* was 34.67 years (SD = 14.55). Clinical features of complicated malaria in patients of all the three groups at presentation are shown in Fig. 1. The sex distribution of the study population is shown in Fig. 2. Symptoms such as acute respiratory distress syndrome, disseminated intravascular coagulation (DIC) and coma, known to be features of severe malaria were not observed in any of the patients in the present study. The baseline characteristics of all the study patients are shown in Table 1. These characteristics in each of the three groups have been shown in Table 2. There was no mortality in any of the three groups. Application of one-way ANOVA-*F* test shows a high-significant difference among different groups for infection with *P. vivax*, *P. falciparum* and co-infection at 5 % level of

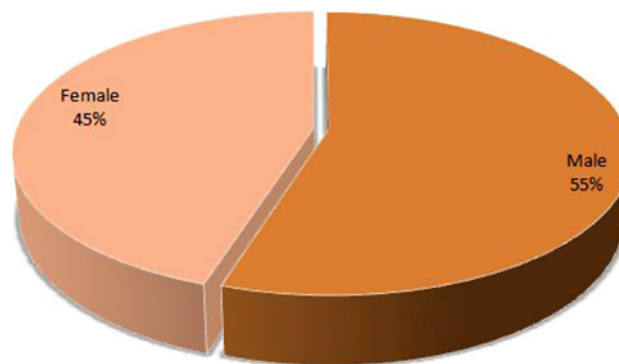


Fig. 2 Pie chart showing the distribution of males and females in the study population

significance ($p < 0.05$). A comparison of the characteristic features of patients of *P. falciparum* and *P. vivax* is shown in Table 3. Thirteen patients with *P. falciparum* and 9 patients with *P. vivax* having acute kidney injury were given renal replacement therapy in the form of hemodialysis. All the patients who were dialyzed had an uneventful recovery. Patients with severe anemia (hemoglobin <5 mg/dl) and thrombocytopenia (platelet count <150,000/mm³), who were hemodynamically unstable were given packed red blood cells and platelets transfusions respectively. On discharge, patients who were infected with *P. vivax* alone and those who had *P. falciparum* co-infection as well, were given a treatment of primaquine in a dosage of 15 mg/day in two divided doses for 14 days. A prior blood G6PD level was obtained before starting primaquine.

Discussion

Malaria is one of the major public health problems of India. Around 1.5 million confirmed cases are reported annually

Fig. 1 Clinical features of complicated malaria in patients of all the three groups at presentation

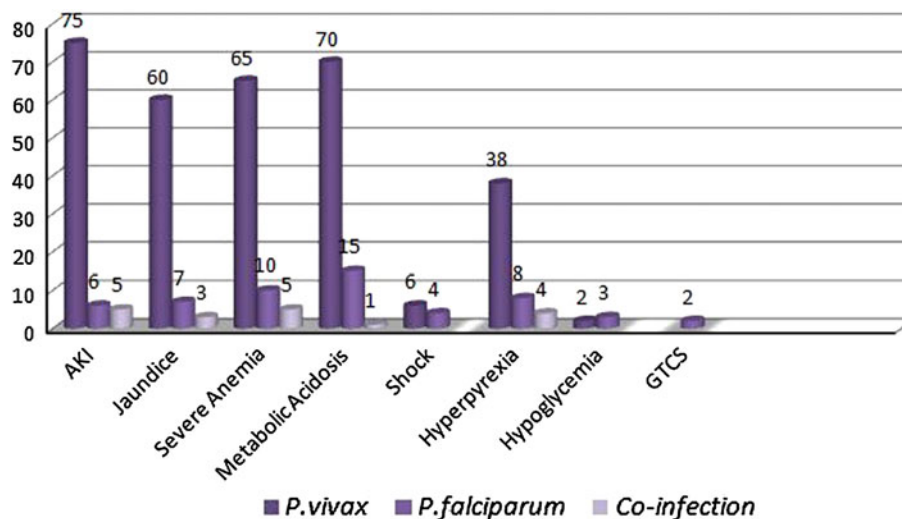


Table 1 The baseline characteristics of all the patients in study group

	Mean	Standard deviation
Age (years)	34	14
Haemoglobin (g/dl)	6.31	3.2
Platelets (per mm ³)	124352	76100.8
Blood urea (mg/dl)	87	54.6
Serum creatinine (mg/dl)	3.2	1.91
Total bilirubin (mg/dl)	3.31	2.4
Direct bilirubin (mg/dl)	2.3	1.69
Indirect bilirubin (mg/dl)	0.98	0.87
SGOT (U/l)	70.56	65
SGPT (U/l)	56.89	46
Serum ALP (U/l)	99.98	38.3
pH	7.23	0.14
Temperature (°F)	100.91	1.22

Table 2 The baseline characteristics of patients in three groups

	<i>P. vivax</i>	<i>P. falciparum</i>	Co-infection
Acute kidney injury	75	6	5
Jaundice	60	7	3
Severe anemia	65	10	5
Metabolic acidosis	70	15	1
Shock	6	4	–
Hyperpyrexia	38	8	4
Hypoglycemia	2	3	–
Generalized tonic–clonic convulsions	–	2	–

by the National Vector Borne Disease Control Programme, of which about 50 % are due to *P. falciparum* (NMRI, New Delhi 2012). Malaria is completely curable provided effective treatment is started early. Delay in treatment may lead to serious consequences including death. Fever is the cardinal symptom of malaria. It is often associated with chills, rigors, headache, myalgia, arthralgia, anorexia, nausea and vomiting. Symptoms of malaria can often be non-specific and mimic other diseases like viral infections, enteric fever etc. These observations are largely based on a number of case reports worldwide and two recently reported large case series from Papua New Guinea (Genton et al. 2008) and Indonesia (Tjitra et al. 2008).

Malaria should be suspected in patients residing in endemic areas and in those patients who have recently visited an endemic area. All clinically suspected malaria cases should be investigated immediately by microscopy and/or Rapid Diagnostic Test. Complications in severe malaria are either sequestration related, such as cerebral malaria, renal dysfunction, hepatic dysfunction, and

Table 3 Mean (SD) of patients infected with *P. falciparum* and *P. vivax* and *p* value of comparison between the two groups

	<i>P. falciparum</i>	<i>P. vivax</i>	<i>p</i> value
Age (years)	34.16 (13.3)	34.85 (14.5)	0.806
Hemoglobin (g/dl)	7.18 (3.69)	5.84 (2.9)	0.073
Platelets (per mm ³)	149833.3 (102188.2)	119323.6 (70498.4)	0.132
Blood urea (mg/dl)	101.54 (58.78)	83.16 (52.09)	0.127
Serum creatinine (mg/dl)	2.48 (2.16)	3.72 (1.70)	0.005
Total serum bilirubin (mg/dl)	2.86 (1.73)	3.64 (2.58)	0.054
Direct bilirubin (mg/dl)	2.05 (1.27)	2.53 (1.83)	0.100
Indirect bilirubin (mg/dl)	0.78 (0.62)	1.11 (0.95)	0.028
SGOT (U/l)	77.5 (57.48)	63.87 (65.10)	0.269
SGPT (U/l)	50.23 (24.42)	57.41 (52.58)	0.286
Serum alkaline phosphatase (U/l)	98 (57)	101.54 (33.4)	0.747
pH	7.34 (0.10)	7.24 (0.13)	0.000
Temperature (°F)	101 (1.34)	101.59 (1.20)	0.692

ARDS, or non-sequestration related, such as anemia and thrombocytopenia. Non-sequestration-related complications are found frequently in *P. vivax* infection. However, for sequestration-related complications, it was always presumed that coexisting *P. falciparum* infection may evade appearance in blood film because of heavy sequestration. The most common complications observed in the present study were jaundice and hepatic dysfunction, which are similar to the reported observations in severe *P. falciparum* malaria and *P. vivax* malaria in this region (Kochar et al. 2003a, b, 2005, 2006; Nautiyal et al. 2005). Acute kidney injury, which was the second most common complication, has also been reported frequently in the Indian subcontinent (Mehta et al. 2001; Mohapatra et al. 2002; Kochar et al. 2005). In our study acute kidney injury was observed in 75 patients in the *P. vivax* group, 6 patients in *P. falciparum* group and in 5 patients in the co-infected group. Cerebral malaria was observed in five patients; this has also been reported in one patient in Pakistan (Beg et al. 2002) and in three patients in India (Kochar et al. 2005) in malaria caused by *P. vivax*. Status epilepticus has also been reported in Turkey (Ozen et al. 2006) and India (Kochar et al. 2007a, b). In our study generalized tonic–clonic convulsions were observed in two patients infected with *P. falciparum*. Other reported neurologic manifestations include acute inflammatory demyelinating polyneuropathy (Chakravarty et al. 2004) and post-malaria neurologic

syndrome causing bilateral facial paralysis (Kochar et al. 2007a, b), have not been reported in the present study.

Pulmonary syndromes associated with *P. vivax* malaria include acute non-cardiogenic pulmonary edema, ARDS, acute pulmonary injury, and interstitial pneumonia (Parren et al. 1998; Tanios et al. 2001; Habib and Singh 2004; Kochar et al. 2005; Taylor et al. 2006). These syndromes are also associated with high mortality rates for *P. falciparum* malaria and were the most commonly observed *P. vivax*-associated complications in the study in Papua New Guinea (Genton et al. 2008). Anemia was the most commonly observed complication in a recent study from Indonesia (Tjitra et al. 2008). Recent observations have shown evidence of sequestration of parasites in lung vasculature during evaluation of lung injury in *P. vivax* malaria (Nicholas et al. 2007). Cerebral dysfunction in *P. vivax* malaria may occur through generation of nitric oxide (Beg et al. 2002). Cytokines and leukotrienes may be responsible for severe anaemia and hemostatic complications (Clark and Cowden 1999). A report of *P. vivax* infection in pregnancy that resulted in low birth weight babies suggested sequestration of *P. vivax* in the placenta (Nosten et al. 1999). A recent study that analyzed malaria severity in *P. vivax* infection clearly demonstrated enhanced aggregation, erythrocyte clumping, and reduced deformability affecting microcirculation (Jayavanth and Park 2007). Shock has been reported as a complication of *P. vivax* malaria Kumar et al. (2007). In the present study 6 patients infected with *P. vivax* presented in shock.

Severe manifestations in *P. falciparum* malaria can develop within 12–24 h and may lead to death, if it is not treated promptly and adequately. Severe malaria is characterized by one or more of the following features: impaired consciousness/coma, repeated generalized convulsions, renal failure (serum creatinine >3 mg/dl), jaundice (serum bilirubin >3 mg/dl), severe anaemia (hemoglobin <5 g/dl), pulmonary oedema/acute respiratory distress syndrome, hypoglycaemia (plasma glucose <40 mg/dl), metabolic acidosis, circulatory collapse/shock (systolic BP <80, <50 mmHg in children), abnormal bleeding and DIC, haemoglobinuria, hyperpyrexia (temperature >106°F or >42 °C), hyperparasitaemia (>5 % parasitized RBCs). The recent years have witnessed an increasing trend of severe malaria caused by *P. vivax*. In the present study, the manifestations of severity were strongly associated with *P. vivax* which included malaria 68.75 % of the total number of cases in the study group.

Conclusions

The present study reflects the association of severe malaria with *P. vivax*. It clearly shows that patients infected with *P.*

vivax also present with manifestations of severe malaria like serum bilirubin >3 mg/dl, serum creatinine >3 mg/dl, severe anaemia (hemoglobin <5 mg/dl), acute kidney injury, metabolic injury, shock, generalized tonic–clonic convulsions and hypoglycemia. The severity of these symptoms shown by *P. vivax* malaria make it quite evident that it must be considered as a cause of severe malaria, which until recently was assumed to be a manifestation of *P. falciparum* malaria.

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