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Original Research Article

Incidence of complications in patients of *Plasmodium vivax* malaria at a tertiary center in northwest India

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ABSTRACT

Background: Malaria is a protozoal disease caused by infection with parasites of *Plasmodium* species, such as *P. vivax, P. falciparum, P. malariae, P. ovale* and *P. knowlesi* through female *Anopheles* mosquito. *Plasmodium vivax* alone causes 60 to 65% of infections in India. The main objective of the study was to observe various complications in the patients affected with *P. vivax* malaria and to analyse the clinical, hematological and biochemical profile of these patients.
Methods: A non-randomized prospective study was carried out on 170 patients with acute febrile illness admitted in the department of Medicine, SMS Hospital, Jaipur during period from October 2011 to September 2012 presented The infection was confirmed by detection of parasite (for *P. vivax*) in peripheral blood film by thick and thin slide methods and rapid diagnostic test (Optimal test).
Results: Male preponderance was seen in the study. Death was noted in 5 (3%) patients. Thrombocytopenia (85%) was the most common finding observed. Level of serum creatinine was more than 1.5 mg/dl in 34.7% patients. Thirty-one patients (18.23%) had severe anaemia (Hb <6 gm/dl). Severe hypoglycemia was observed in 19 patients (<40-60 mg/dl). Acute renal failure was common comorbidity observed in majority of the patients. Mean LDH value was significantly higher in patients with hepatitis and anemia.
Conclusions: The clinical pattern of *P. vivax* monoinfection has changed recently. Every patient of *P. vivax* malaria should be evaluated thoroughly for clinical or biochemical evidence of any complications and patients presenting with complications should managed as per guidelines of severe malaria.

Keywords: Complications, Malaria, *Plasmodium vivax*

INTRODUCTION

Malaria is a protozoal disease caused by infection with parasites of the genus *Plasmodium*, mainly five types of *Plasmodium* species such as *P. vivax, P. falciparum, P. malariae, P. ovale, and P. knowlesi* are known to cause malaria in humans. These parasites are transmitted through certain species of infected female *Anopheles* mosquito. Malaria, among the other six diseases like diarrhoea, HIV/AIDS, tuberculosis, measles, hepatitis B and pneumonia account for 85% of global infectious disease burden and imposes great socio-economic burden on humanity. About 36% of the world population, i.e., 2020 million is exposed to the risk of contracting malaria in ~90 countries. World Health Organization estimates 300-500 million malaria cases annually, in addition, the estimated annual mortality attributed to malaria ranges from 1.5 and 2.7 million globally.[1,2]

About 2 million confirmed malaria cases and 1,000 deaths are reported annually, although 15 million cases and 20,000 deaths are estimated by WHO South East

Asia Regional Office. India contributes 77% of the total malaria in South East Asia.[3-5] Rajasthan accounts about 4% cases of total malaria cases in India.[3] In India 60 to 65% of the infections are due to *P. vivax* and 35 to 40% due to *P. falciparum*.

Complications are well known associated with *P. falciparum* while *P. vivax* infection is usually have benign course and complications was not known to associated.[6-8] Some organ specific studies have shown that the inflammatory response during *P. vivax* infection is greater than that seen in *P. falciparum*. It also have lower pyrogenic threshold. There is although low parasetemia but because of its tendency to destruct more non-infected RBC which could be probable mechanism for severe anemia. Acute respiratory distress syndrome (ARDS) may be due to cytokine related increase in alveolar permeability and altered alveolar fluid clearance. Peripheral destruction and splenic sequestration of platelets leading to acute microvascular thrombosis and endothelial injury causes thrombocytopenia and acute renal failure.[5,9,10]

The course of *P. vivax* malaria is changing from benign to severe due to involvement of multiple organ dysfunction. The current study was done with the objective to analyse clinical and laboratory profile of patients admitted with severe *P. vivax* malaria along with its complications and outcome.

METHODS

This was a non-randomized prospective study carried out on 170 patients presented with acute febrile illness in the Department of Medicine at SMS hospital, Jaipur during period of October 2011 to September 2012. The illness was confirmed by detection of parasite (for *P. vivax*) in peripheral blood film by thick and thin slide methods and rapid diagnostic test (Optimal test).

Inclusion criteria

Patients with peripheral blood film positive for *P. vivax* parasite and patients' willingness to participate in the study.

Exclusion criteria

Patients with peripheral blood smear negative for *P. vivax* parasite in three consecutive samples at the interval of twelve hours apart, patients with peripheral blood smear or rapid diagnostic test positive for *P. falciparum* or for both, patients with other febrile illness like dengue fever, viral hepatitis, HIV and meningitis, patients with chronic illness like chronic renal failure, chronic liver disease and patients with known bleeding diathesis or malignant disease.

Detailed history of the patients was collected in a predesigned proforma. All the patients underwent complete clinical examination including routine hematological, biochemical and imaging procedures.

After explaining the methodology of the study to patients and attendants comprehensive history along with thorough clinical examination were recorded and blood samples were collected for analysis first within 24 hours of admission before the initiation of antimalarial treatment, then on second day and subsequently further tests were carried out under supervision in the Central Laboratory SMS Hospital Jaipur. Both thick and thin films were made at the time of admission. The thick film was used for detection of infection and thin film used to identify the species. It was further tested with rapid diagnostic tests (optimal test) in Central laboratory, SMS Hospital.

Hematological investigations include serum hemoglobin and biochemical investigations include blood sugar, serum urea, serum creatinine, serum bilirubin, SGOT, serum LDH, etc. Chest X-ray were also done in all patients.

The data collected was tabulated and analysed using Microsoft Excel and the values were presented in number and percentages.

RESULTS

In this study, a total of 170 patients studied for *P. vivax* malaria cases were included. Majority of them were (88; 51.7%) below thirty years of age. Table 1 show that 55% of all *P. vivax* malaria patients were males.

Table 1: Distribution of *P. vivax* malaria patients according to age and sex (n=170).

Age (years)	Female (%)	Male (%)
≤20	19 (11.18)	17 (10.00)
21-30	23 (13.53)	29 (17.06)
31-40	22 (12.94)	17 (10.00)
41-50	5 (2.94)	10 (5.88)
>50	10 (5.88)	18 (10.59)
Total	79 (46.47)	91 (53.53)

In the study, thrombocytopenia (85%) was the most common finding observed followed by hepatitis (33.5%). Acute renal failure (ARF) was present in 17% patients, pulmonary involvement was seen in 17.6%, spontaneous bleeding in 14% patients. Neurological involvement was observed in 14.7% patients and severe anemia in 10.6% patients. (Table 2).

Serum bilirubin level above 3 mg/dl was observed in 44 (26%) patients and 66 (39%) patients had more than 2 mg/dl. The serum transaminases level was more than 35 IU in 149 (87%) patients. Level of serum creatinine was more than 1.5 mg/dl in 59 (34.7%) patients. Majority patients (66; 39%) had platelet count of 21,000-40,000

per cumm. With regard to hemogram of patients with *P. vivax* 18 (10.6%) patients had hemoglobin concentration <5 gm/dl. Thirty-one patients (18.23%) had serum hemoglobin less than 6 gm/dl and 62 (36.5%) patients had serum hemoglobin of less than 8 gm/dl.

Table 2: Various complications in *P. vivax* malaria patients (n=170).

Complications	No. of patients (%)
Bleeding tendency	24 (14)
Cerebral malaria	25 (14.7)
Pulmonary involvement	30 (17.6)
Acute renal failure	29 (17)
Hepatitis	57 (33.5)
Anaemia	18 (10.6)
Hypoglycemia	2 (1.17)
Hypotension	32 (18.9)
Thrombocytopenia	145 (85)
Mortality	5 (3)

Of total 170 patients, 30 (17.6%) had pulmonary complication. Of them, 4 (2.3%) patients had ARDS picture in chest X-ray and 16 (9.4%) patients had pneumonitis picture in chest X-ray and 10 (5.8%) patients had pleural effusion either detected in chest X-ray or USG. Among 170 patients, 32 patients were identified with hypotension (<90 mmHg).

Cerebral malaria was diagnosed in 25 (14.71%) patients. Severe hypoglycemia was observed in 19 patients (<40-60 mg/dl).

Table 4 presents the spectrum of symptom combinations of severe manifestation in malaria patients. Out of 170 patients, 65 patients with malaria had shown more than 2 associated complications. Acute renal failure was common comorbidity observed in majority of the patients.

In our study, mortality was noted in 5 patients. Of total 5 patients who expired 2 had ARDS, one had bilateral pleural effusion, 4 patients had altered sensorium, hepatic dysfunction was present in 4 patients while all patients had serum bilirubin more than 2.5 mg/dl and 4 patients had more than 3 mg/dl. 3 patients were in shock, 1 patient had severe anemia and 2 patients had bleeding.

P value was <0.05 for patients with pulmonary manifestation, jaundice, altered sensorium and hypotension (Table 5).

Mean LDH value in all patients positive with *P. vivax* was 856. The value was significantly higher in patients with hepatitis and anemia (P value= 0.03). The mean LDH level was 1125 in patients with serum SGOT level >175 IU, 1139 in patients with serum bilirubin level >3 mg/dl, and 1603 in patients with severe anemia (Table 6).

Table 3: Biochemical, hematological and clinic findings among patients.

Variable	No. of patients (%)
Serum bilirubin level (mg/dl)	
>15	4 (2.35)
10-14.9	5 (2.94)
5-9.9	15 (8.82)
3- 4.9	20 (11.76)
2-2.9	23 (13.5)
Serum transaminase levels	
>400	2 (1.18)
300-400	4 (2.35)
200-299	17 (10)
100-199	28 (16.47)
>35	98 (57.65)
Serum creatinine (mg/dl)	
>5	10 (5.9)
3-4.9	19 (11.2)
2-2.9	12 (7)
1.5-1.9	18 (10.6)
Platelet count (per cumm)	
<10,000	10 (5.88)
11,000-20,000	22 (13)
21,000-40,000	66 (39)
41,000-60,000	28 (16.5)
60,000-1 lakh	19 (11.2)
>1 lakh	25 (14.7)
Hemoglobin concentration (g/dl)	
<5	18 (10.6)
5-6	13 (7.64)
6-8	31 (18.23)
8-10	52 (30.6)
>10	56 (33)
Pulmonary manifestation	
ARDS	4 (2.35)
Pneumonitis	16 (9.41)
Pleural effusion	10 (5.88)
Hypotension <90 mm Hg	
Present	32 (18.82)
Absent	138 (81.18)
Cerebral malaria	
Present	25 (14.71)
Absent	145 (85.29)
Blood glucose level (mg/dl)	
<40	2 (1.18)
<50	5 (2.94)
50-60	13 (7.64)
>60	150 (88.24)

DISCUSSION

In the past few years, many cases of *P. vivax* malaria were found some cases resulted in mortality. The reported severe manifestations were hepatic dysfunction, renal dysfunction, severe anaemia, cerebral malaria and

ARF and multiple organ involvement in severe cases.[11] Hence the current study was done with the objective to find out various complications related to *P. vivax* malaria fever and its related outcome.

Table 4: Spectrum of symptom combinations of severe manifestation in malaria patients.

Co-morbidities	No. of patients
PM+CM+JND+ARF+HB+BLD	2
PM+JND+ARF+CM	4
PM+ARF+CM	6
CM+JND+ARF	8
PM+JND+ARF	8
JND+ARF+BLD	5
ARF+PM	12
ARF+JND	19
PM+JND	14
JND+Thrombocytopenia	39
ARF+Thrombocytopenia	23
Overall ≥2 organ involvement	65
NO organ involvement	25
One organ involvement	75

PM- pulmonary involvement, JND- jaundice, CM- cerebral malaria, BLD- bleeding, Hb- hemoglobin, ARF- acute renal failure.

Table 5: Profile of malaria patients expired with various manifestations (n=170).

	Survived (N)	Expired (N)
PM		
Absent	138	2
Present	27	3
ARF		
<3 mg/dl	138	3
>3 mg/dl	27	2
JND		
<3 mg/dl	125	1
>3 mg/dl	40	4
CM		
Absent	144	1
Present	21	4
BLD		
Absent	143	3
Present	22	2
Hypotension		
Absent	136	2
Present	29	3
Hb		
>5 gm%	148	4
<5 gm%	17	1

PM: pulmonary involvent; ARF: Acute renal failure; JND: jaundice; CM: cerebral malaria; BLD: bleeding; Hb: hemoglobin.

In this study, total patients studied for *Plasmodium vivax* malaria cases were 170 patients. 79 (45%) were females and 91 (55%) were males. Thrombocytopenia was the most common finding. 145 (85.26%) patients had platelet count <1 lakh/cm^3. 32 (19%) patients had platelet count <20,000 per cumm and 24 (14.1%) patients had spontaneous bleeding and required platelet transfusion. However, Naha et al reported thrombocytopenia in 86.4%, George et al found 93.3% of their patients to be having thrombocytopenia, Singh et al and Sharma et al reported thrombocytopenia in 96 and 96.3% of patients, respectively.[12-15] In studies conducted by Kochar et al and Mohapatra et al thrombocytopenia was not as common as in the above mentioned studies it was found to be in 12.5% and 3.6% patients, respectively.[16,17]

Table 6: Mean serum LDH level associated with various complications in study participants.

	Mean LDH values (IU)
SGOT	
<175 IU	801
>175 IU	1125
Pulmonary involvement	
Absent	814
Present	1054
S. bilirubin	
<3 mg/dl	757
>3 mg/dl	1139
S. creatinine	
<3 mg/dl	816
>3 mg/dl	1052
Altered sensorium	
Absent	855
Present	864
Hb	
>5 gm%	768
<5 gm%	1603
Hypotension	
Absent	850
Present	881
Bleeding	
Absent	829
Present	1020

SGOT: serum glutamic-oxaloacetic transaminase; Hb: haemoglobin.

Hepatic dysfunction was the second most common finding after thrombocytopenia. Serum bilirubin was >3 mg/dl in 44 (26%) patients. Serum bilirubin was observed mostly of unconjugated type and has been attributed to excessive hemolysis of both infected and uninfected RBCs due to high inflammatory reaction. But presence of conjugated hyperbilirubenemia with raised serum transaminases suggest that there was also direct hepatic damage due to hepatocyte destruction. 31 patients out of 170 had serum transaminases level >175 IU i.e., >5 times of normal upper limit. Kochar et al reported hepatic dysfunction in 57.5% of patients, George et al found liver dysfunction in 43.3%. Singh et al, Sharma et al, Mohapatra et al and Hazra et al found liver dysfunction in

17.3%, 27.1%, 7.2%, and 9.09% of patients, respectively.[14-19]

In our study on hematological examination severe anemia (<5 gm/dl) was detected in 19 (10.6%) patients. 31 (18.23%) patients had serum hemoglobin less than 6 gm% and 62 (36.5%) patients had serum hemoglobin of less than 8 gm%. Anemia was also very common finding in other studies.[8,9] Anemia with *Plasmodium vivax* is due to greater removal of infected and non-infected RBC as explained by Dougles et al.[20]

Serum LDH level was frequently elevated and was more common in patients with severe malaria. 47% patients had serum LDH level more than 600 IU. LDH level was very high in patients with severe anemia, renal failure, hepatitis, and ARDS. LDH may rise because of severe hemolysis, convulsions causing muscular strain, hepatocyte damage, from lungs and kidney cell breakdown.[21] Mean LDH in *Plasmodium vivax* malaria was 856 IU while it is increased to 1125 IU in patients with SGOT level >175 IU, 1054 in patients with pulmonary involvement, 1139 IU in patients with serum bilirubin >3 mg/dl, 1052 in patients with renal failure and 1603 IU patients with severe anemia.

Ten cases out of 170 admitted patients positive with *Plasmodium vivax* had serum creatinine greater than 5 mg/dl, and of these patients 3 patients require renal replacement therapy. In the study of Nadkar et al showed that 31% patients with *P. vivax* had serum creatinine more than 3 mg/dl.[22] Kochar et al showed 42% patients of severe malaria positive with *P. vivax* had acute renal failure and these findings were much higher than obtained in our study.[16]

Four 4 out of 170, had ARDS picture in X-ray, 9% patients had pneumonitis pattern while 6% patients had pleural effusion. Pulmonary involvement in *Plasmodium vivax* may be because of cytokine related increase in alveolar permeability and altered alveolar fluid clearance.[23] Of total 5 patients who expired 2 had ARDS, one had bilateral pleural effusion along, 4 patients had altered sensorium, acute renal failure was present in 2 patients, hepatic dysfunction was present in 4 patients while all patients had serum bilirubin more than 2.5mg/dl and 4 patients had more than 3 mg/dl. Three patients was in shock, 1 patients had severe anemia and 2 patients had bleeding. Pulmonary manifestation, hepatic dysfunction, altered sensorium and hypotension was statistically related with increased mortality. Only 2 patients had very low value of blood glucose (hypoglycemia), i.e., <40 mg/dl. 7 patients had blood glucose level <50 mg/dl and 20 patients had blood glucose level <60 mg/dl. It may be because of IV fluids (dextrose or dextrose saline) are administered in emergency department before patients reach in ward and before blood sample was taken. In the study by Nadkar et al mortality was 10% while in our study mortality was 3%.[22]

CONCLUSION

In our study complications was very common with *Plasmodium vivax* patients. Associated complications was hepatitis, thrombocytopenia, bleeding, renal failure, severe anemia, shock, ARDS, hypoglycemia, MODS etc. Though *P. vivax* was thought to be benign, recent studies have demonstrated it has an immense potential to cause life threatening complications and even death. Every patient of *P. vivax* malaria should be evaluated thoroughly for clinical or biochemical evidence of any complications and patients presenting with complications should be admitted and managed as per guidelines of severe malaria.

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