# Study Of Clinical Spectrum And Complications Of Plasmodium Vivax Malaria

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**Abstracts:** Objectives: To study the clinical spectrum and complications of plasmodium vivax malaria. Methods: The study has been carried out at Shree Sayajirao General Hospital and Medical College Baroda. A total of 200 patients admitted to the hospital with fever of > 38.5 degree Celsius and peripheral smear positive for plasmodium vivax were included in study. Patients with plasmodium falciparum, plasmodium ovale, plasmodium malariae infection were excluded from study. History, examination and needed investigations were done. Results: 1) A total of 200 patients of P.vivax malaria infections were included in this study.2) Plasmodium vivax malaria was more common in males. Majority of the patients belonged to second decade of life.3) All patients presented with fever. The incidences of other symptoms were headache (22.5%), vomiting (36%), jaundice (40.5%) and pain abdomen (26%). 4) The incidences of associated clinical findings were pallor (20.5%), icterus(41%), hepatomegaly (53%) and splenomegaly (47%). 5) Severe thrombocytopenia was seen in 37%, hyperbilirubinemia in 26.5%, leukocytosis in 6.5% and metabolic acidosis in 5 % of the cases. 6) Cerebral malaria was seen in 3.5 % of the study population. 7) Acute kidney injury was present in 3% of the cases. 8) ARDS was seen in 8.5 % of the cases. 9) Multi organ dysfunction was seen in 3 % cases (6 patients) of which 4 patients succumbed to the illness.Conclusion: This study show that Plasmodium vivax malaria can also have a severe and complicated course which is usually associated with Plasmodium falciparum malaria. Thrombocytopenia and hepatic dysfunction are commonly seen and are early indicators for the severity of the disease. Life threatening complications such as ARDS, AKI, cerebral malaria and MODS do complicate benign tertian malaria as seen in our study. [Vishakha A NJIRM 2017; 8(1):120-125]

**Key Words:** plasmodium vivax malaria, acute respiratory distress syndrome, acute kidney injury

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**Introduction:** Malaria is a protozoan disease transmitted by the bite of infected *Anopheles* mosquitoes. The most important of the parasitic diseases of humans, it is transmitted in 108 countries containing 3 billion people and causes nearly 1 million deaths each year [1]. P.vivax is geographically more widely distributed with up to 2.5 billion people at risk and an estimated 7080 million cases every year. Although P.vivax malaria has a huge burden on the health, longevity and general prosperity of the people, research on vivax malaria and its complications are grossly overlooked and left in the shadow of the enormous problem caused by P.falciparum. Recent studies have shown that complications associated with P.vivax are on the rise and outcomes are similar to that of P.falciparum malaria [2]. Hence a study on the complications of P.vivax malaria would help gather information on the morbidity caused by the disease and help reduce the burden and unexpected mortality due to the disease.

Severe malaria is generally caused due to P.falciparum infections. There have been scattered reports in the last 30 years of P.vivax causing cerebral malaria, thrombocytopenia, disseminated intravascular coagulation (DIC), ARDS, and renal failure. Cerebral malaria is generally due to P.falciparum infection. However, there have been case reports of neurological impairment in P.vivax malaria [3-11]

**Objectives:**

1. To study the clinical spectrum of plasmodium vivax malaria.
2. To study the complications of plasmodium vivax malaria

**Methods:** This study was prospective study done over a period of one year from October 2013 to September 2014 with permission of IRB and consent of subjects. .The study has been carried out at Shree Sayajirao General Hospital and Medical College Baroda.A total of 200 patients admitted to the hospital with fever of > 38.5 degree Celsius and peripheral smear positive for plasmodium vivax were selected. They were followed from admission till recovery, discharge or death which ever was earlier.

**Diagnosis:** Demonstration of the parasite: peripheral smear: Light microscopy of Giemsa stained blood smears is the accepted standard for malaria diagnosis. Both thin and thick smear examined.

Thin smear : should be rapidly air dried, fixed in anhydrous methanol, and stained and RBC's in the tail

of the smear should be examined under oil immersion (1000 magnification). The level of parasitemia is expressed as number of parasitized erythrocytes per 1000 RBCs, or per 200 WBCs, and this figure is converted to number of parasitized erythrocytes per micro litre. Thick smear: should be of uneven thickness, and it should be dried thoroughly, and stained without fixing. As many layers of RBCs overlie one 35 another and are lysed during the staining, hence the thick film has the advantage of concentrating the parasites (by 2040fold) and thus increasing the diagnostic sensitivity. Both parasites and WBCs are counted and the number of parasites per unit volume is calculated from the total leukocyte count.[20]

Proper history taking and examination were done in all patients. Complete blood count, peripheral smear, random blood glucose, liver function test, renal function test, prothombin time were done in all patients. In selected cases chest x ray, blood culture, cerebrospinal fluid analysis, arterial blood gas analysis was done.

Patients with plasmodium falciparum, plasmodium ovale, plasmodium malariae infection were excluded from study.Indicators of severe malaria and poor prognosis according to the world health organisation[21]

| Signs | Manifestations |
|---|---|
| Cerebral malaria /Unarousable coma | Failure to localise or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion |
| Severe anaemia | Hematocrit <15% or hemoglobin < 50 g/L |
| Renal failure | Urine output <400 ml/24 hours and a serum creatinine >265 µmol/l (> 3.0 mg/dl) despite adequate volume repletion |
| Pulmonary edema and acute respiratory distress syndrome | Non cardiogenic pulmonary edema, often aggravated by overhydration |
| Hypoglycemia | Whole blood glucose concentration <2.2 mmol/l (<40 mg/dl) |
| Acidemia/acidosis | Arterial pH <7.25 or acidosis (plasma bicarbonate <15 mmol/l) |
| Hypotension/shock | Systolic blood pressure <70 mmHg |
| Bleeding/DIC | Significant bleeding from gums, nose, gastrointestinal tract ± evidence of DIC |
| Convulsions | More than two generalized convulsions seizures in 24 hours |
| Hemoglobinuria | Macroscopic black, brown or red urine; |
| Extreme weakness | Prostration; inability to sit unaided |
| Jaundice | S.bilirubin > 50 mmol/L (>3 mg/dL) if combined with other evidence of vital organ dysfunction |

**Result:** A total of 200 patients of P.vivax malaria infections were included in this study.

**Table: 1 Clinical spectrum of disease: common symptoms observed in patients of P.vivax malaria infections were observed as below. Fever, abdominal pain , yellowish discoloration of urine and sclera ,vomiting were common symptoms.**

| | No. of Patients | % |
|---|---|---|
| Fever | 200 | 100 |
| Jaundice | 81 | 40.5 |
| Vomiting | 72 | 36 |
| Headache | 45 | 22.5 |
| Pain in abdomen | 52 | 26 |
| Cough | 25 | 12.5 |
| Breathlessness | 12 | 6 |
| Bleeding | 12 | 6 |
| Altered sensorium | 6 | 3 |
| Oliguria | 5 | 2.5 |
| Petechia | 4 | 2 |
| Convulsion | 1 | 0.5 |

**Table: 2: clinical signs of general examination pallor, icterus, pedal edema were noted in all patients. Organomegaly in gastrointestinal system, sign of respiratory distress and altered level of consciousness in nervous system were noted.**

| | No. Of Patients | % |
|---|---|---|
| Pallor | 41 | 20.5 |
| Icterus | 82 | 41 |
| Pedal Edema | 2 | 1 |
| Spleenomegaly | 94 | 47 |
| Hepatomegaly | 106 | 53 |
| Respiratory signs | 37 | 18.5 |
| CNS Manifestations | 7 | 3.5 |

Various hematological investigations were done in all patients to measure the severity of disease and to observe various systemic complications.

**Table 3: Hemoglobin levels in all patients were done to observe the severity of anemia as hematological complication.**

| Haemoglobin level | No. Of Patients | % |
|---|---|---|
| <5gm/dl | 2 | 1 |
| 5.1-11.9 gm/dl | 72 | 36 |
| >12 gm/dl | 126 | 63 |

**Table 4: Platelet counts in all patients were done to observe thrombocytopenia as hematological complication.**

| Platelet count | No. Of Patients | % |
|---|---|---|
| <50,000 | 74 | 37 |
| 50,000-1 lac | 74 | 37 |
| 1-1.5 lac | 35 | 17.5 |
| >1.5 lac | 17 | 8.5 |

**Table 5: Total Leukocyte counts in all patients were done to note leucocytosis or leucopenia as hematological complication.**

| Total count | No. Of Patients | % |
|---|---|---|
| <3.9*1000 | 49 | 24.5 |
| 4-11.9*1000 | 140 | 70 |
| >12*1000 | 11 | 5.5 |

**Table 6: Differential Leukocyte counts result were obtained as below.**

| | Mean | SD | Range |
|---|---|---|---|
| Total WBC | 6148 | 4076 | 2600-42,000 |
| Polymorphonuclear cells | 75.2 | 11.12 | 40-96 |
| Lymphocytes | 20.37 | 10.58 | 1-52 |
| Eosinophils | 1.71 | 1.93 | 0-22 |
| Monocytes | 2.78 | 1.86 | 0-13 |

**Table 7: Serum bilirubin level were observed in all patients as injury to hepatic parenchyma and cholestasis may cause hepatitis, jaundice and in severe cases hepatic encephalopathy.**

| S. bilirubin level | No. Of Patients | % |
|---|---|---|
| <2.9 mg/dl | 147 | 73.5 |
| 3-5.9mg/dl | 46 | 23 |
| >6mg/dl | 7 | 3.5 |

**Table 8: Prothrombin time in study were done to measure the acute hepatic injury .**

| PT INR | No. Of Patients | % |
|---|---|---|
| <13.5 sec | 137 | 68.5 |
| >13.5 sec | 63 | 31.5 |

**Table 9: CNS Manifestations convulsion and altered sensorium as sign of cerebral malaria was observed in all patients.**

| Cerebral malaria | No. Of Patients | % |
|---|---|---|
| Altered sensorium | 6 | 3 |
| Seizures | 1 | 0.5 |

**Table 10: Respiratory manifestations in form acute bronchitis and severe complication of ARDS were assessed in all patients.**

| Respiratory manifestations | No. Of Patients | % |
|---|---|---|
| Bronchitis | 25 | 12.5 |
| ARDS | 17 | 8.5 |

**Table:11: severe complications of malaria contributing to increased morbidity and mortality in patients other than respiratory and CNS including acute kidney injury ,metabolic acidosis , multiorgan failure with mortality were assessed.**

| Other complications | No. Of Patients | % |
|---|---|---|
| Acute kidney injury | 6 | 3 |
| Metabolic acidosis | 10 | 5 |
| MODS | 6 | 3 |
| Mortality | 4 | 2 |

**Discussion:** Clinical spectrum : sign and symptoms: In our study, fever was the presenting symptom in all the patients. This finding correlates with the results obtained from studies conducted by Song et al at Chuncheon, Korea[12] that fever is common presenting symptom of malaria.

Vomiting and pain abdomen: were observed in 36% and 25.6 % respectively of the patients in our study. It was seen in 39% and 34 % of the patients in the study

conducted by Echevveri et al at Columbia[13]. Explaining gastrointestinal involvement in malaria as hepatomegaly, spleenomegaly and gastritis.

Headache was present in 22.1 % cases in our study and was seen in 83.2 % of the cases in the study done by Shin et al at Republic of Korea[14]. Headache with vomiting may be initial symptom of cerebral malaria.

Cough and breathlessness were seen in 8.5% of the patients in our study.It correlates with the study conducted by Kochar et al at Bikaner[2] in which 10 % of the patients had these symptoms. Respiratory symptoms of cough and breathlessness as presenting symptom of complications acute bronchitis and ARDS were present in our 8.5% of patients.

Neurological involvement in the form of seizures and altered sensorium were observed among 3.5 % of the patients in our study while in the study done by Naha et al at Mangalore[15], it was seen in 1.41 % cases. The results varied with the study done by Kochar et al at Bikaner [2] where the incidence was 12.5%. The higher incidence of cerebral malaria in their study was due to the fact that only patients were included, whereas our study included all P.vivax malaria cases. Cerebral malaria is seen also in complicated P. vivax malaria which is more common in P. falciparum malaria. Cerebral malaria manifests as diffuse symmetric encephalopathy where focal neurological signs are unusual but patients may have seizures and altered level of consciousness.[1]

Oliguria as symptom of acute kidney injury was seen in 2.5 % of the patients during the course of hospital stay. This varied with the study by Kochar et al at Bikaner[2], in which the incidence was 45% as they had included only severe P.vivax malaria cases.

Pallor and icterus signs of anemia and jaundice respectively suggestive of hematological and hepatic involvement were present in 20.5 % and 40.5 % respectively in our study, while it was seen in 46 % and 15 % respectively in the study done by Echevveri et al at Columbia[13] .

Hepatomegaly and splenomegaly were noted in 53 % and 47 % respectively in this study. It was seen in 15.8 % and 42 % respectively in the study done by Shin et al at the Republic of Korea[14]. Hepatomegaly and splenomegaly were more common than other systemic involvement.

Renal failure was seen in 3% cases in our study and was found in 10.5 % cases in the study conducted by Andrade et al at Buritus[16]. In the study by Echevveri et al at Columbia [13], no patients had renal dysfunction. Our results varied with the study done by Kochar et al at Bikaner [2] in which a high incidence of 45 % was noted. Renal Impairment is due to erythrocyte sequestration interfering with renal microcirculatory failure and metabolism. [1]

Hepatic dysfunction: Hepatic dysfunction was seen in 26.5 % cases in our study. This correlated with the study done by Sharma et al at Delhi [17].Coagulation profile was deranged in 20% of patients. Liver enzymes were elevated in all the patients. Our results varied with the study done by Kochar et al at Bikaner [2] in which a high incidence of 45 % was noted. In malaria hepatic dysfunction results from hemolysis, hepatocyte injury, and cholestatis. Hepatic dysfunction contributes to hypoglycemia and lactic acidosis.[1]

Acute respiratory distress syndrome: ARDS was seen in 8.5 % cases in our study All 17 patients required ventilatory support, out of which 15 patients had a positive outcome, while 2 patients succumbed to the illness. . In the study done by Kochar et al at Bikaner[2], 10 % cases developed ARDS. The incidence of ARDS in a study done by Andrade et al at Buritus[16] was 21.05 %. Life threatening complication ARDS was observed in patients of P. vivax malaria.Noncardiogenic pulmonary edema is seen in P.vivax malaria. The pathogenesis of this variant of adult respiratory distress syndrome is unclear.[1]

Multi organ dysfunction syndrome: Multi organ dysfunction was seen in 3% in our study, while in the study done by Kochar et al at Bikaner[2], 47.5 % cases had multi organ dysfunction. The higher incidence of all complications (ARDS, AKI, cerebral malaria and MODS) in the study by Kochar et al at Bikaner[2] was due to the fact that only patients who fulfilled the WHO criteria of severe malaria were included in their study, whereas our study included all vivax malaria cases. [21]

Lactic Acidosis is caused by the combination of anaerobic glycolysis in tissues where sequestered

parasites interfere with microcirculatory flow, hypovolemia, lactate production by parasites and a failure of hepatic and renal lactate clearance. Acidosis, an important cause of death from severe malaria.[1]

Mortality: Mortality rate was 2 % (n=4) in our study which correlated to the study done by Sharma et al at Delhi [17].

All four patients had features of sepsis. Death occurred due to AKI, ARDS and hepatic dysfunction in all four patients.

**Investigations:** Severe anemia(HB <6 g/dL): 2 patients had a haemoglobin level less than 6 g/dl in our study. In the study done by Naha et al at Mangalore[15], severe anaemia was seen in 0.47 % cases. Anemia results from accelerated RBC removal by spleen, obligatory RBC destruction at parasite schizogony and ineffective erythropoiesis.[1]

Leucocyte abnormalities: Leucocytosis was seen in 6.5% of the patients in our study whereas 27.5 % had leucopenia .The average leucocyte count was 6634 cell/cumm. In the study by Shin et al in the Republic of Korea[14], 2.9 % had leucocytosis and 19.9 % had leucopenia. Leucocytosis >12,000/microlitre is indicator of poor prognosis in severe malaria.[1]

Thrombocytopenia: Thrombocytopenia (<1.5lakh/µL) was seen in 91 % of the study population, which correlated with the results of the study done by Sharma et al at Delhi[17].Severe thrombocytopenia as per the WHO criteria was found in 37 % cases. Thrombocytopenia with bleeding and DIC is uncommon, seen in <5% of patients.[1]

**Conclusion:**

1. This study highlights the fact that Plasmodium vivax malaria though traditionally considered to be a benign entity can also have a severe and complicated course which is usually associated with Plasmodium falciparum malaria.
2. Thrombocytopenia and hepatic dysfunction are commonly seen and are early indicators for the severity of the disease.
3. Life threatening complications such as ARDS, AKI, cerebral malaria and MODS do complicate benign tertian malaria as seen in our study.

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