

Severe *Plasmodium vivax* Malaria: A Report on Serial Cases from Bikaner in Northwestern India

Dhanpat K. Kochar,* Ashish Das, Sanjay K. Kochar, Vishal Saxena, Parmendra Sirohi, Shilpi Garg,
Abhishek Kochar, Mahesh P. Khatri, and Vikas Gupta

Department of Medicine, S. P. Medical College, Bikaner, Rajasthan, India; Birla Institute of Technology and Sciences, Pilani, Rajasthan, India

Abstract. Epidemiologic studies and clinical description of severe *Plasmodium vivax* malaria in adults living in malaria-endemic areas are rare and more attention is needed to understand the dynamics and its interaction with the immune system. This observational study included 1,091 adult patients admitted to medical wards of S. P. Medical College and associated group of hospitals in Bikaner, India from September 2003 through December 2005. The diagnosis of *P. vivax* malaria was established by peripheral blood film (PBF), rapid diagnostic test (RDT), and polymerase chain reaction (PCR), and severe malaria was categorized as per World Health Organization guidelines. Of 1,091 patients with malaria, 635 had *P. falciparum* malaria and 456 had *P. vivax* malaria. Among patients with severe manifestations, 40 had evidence of mono-infection of *P. vivax* malaria diagnosed by PBF, RDT, and PCR. Complications observed were hepatic dysfunction and jaundice in 23 (57.5%) patients, renal failure in 18 (45%) patients, severe anemia in 13 (32.5%) patients, cerebral malaria in 5 patients (12.5%), acute respiratory distress syndrome in 4 patients (10%), shock in 3 patients (7.5%), and hypoglycemia in 1 (2.5%) patient. Thrombocytopenia was observed in 5 (12.5%) patients, and multi-organ dysfunction was detected in 19 (47.5%) patients. Further large-scale multicentric epidemiologic studies are needed to define the basic pathology of this less known entity.

INTRODUCTION

Plasmodium vivax is the most widely distributed human malaria parasite with an at risk population of 2.5 billion persons. Although the exact burden of disease caused by *P. vivax* infection is still a matter of debate, this parasite causes approximately 100–300 million clinical cases each year. Moreover, the appearance of chloroquine resistance in *P. vivax* parasites, the lack of primaquine alternatives to attack the dormant liver-stage hypnozoites, documentation of cases of severe disease, and increasing temperature caused by climate change increases concern for a future increase of this disease. Although this type of malaria has an enormous burden of disease, research is grossly inadequate because this malaria supposedly causes only benign tertian fever and has an uncomplicated course of illness. However, with implementation of molecular diagnosis, it has become evident that *P. vivax* mono-infection could also be involved in multiple organ dysfunction and severe life-threatening disease as seen in *P. falciparum* infection.^{1,2}

Reported severe manifestations with *P. vivax* mono-infection are similar to those of severe *P. falciparum* infection and include cerebral malaria with generalized convulsions and status epilepticus,^{3–8} severe anemia,^{4,5} hepatic dysfunction and jaundice,^{4,5,9} acute lung injury, acute respiratory distress syndrome (ARDS) and pulmonary edema,^{5,10–14} shock,^{10,15} splenic rupture,¹⁶ acute renal failure,^{4,5,17–20} and severe thrombocytopenia with or without bleeding from different parts of the body.^{5,16,17,21–25}

In most reports, diagnosis was made only by peripheral blood film (PBF) examination and was not supported by molecular diagnostic confirmation, thus allowing potential error in species identification.^{4,5,7–9,11–13,18,20,24} However, some of these studies in the Indian subcontinent have also used confirmation by polymerase chain reaction (PCR).^{3,5,8,10} We report 40 cases of severe *P. vivax* malaria from this region.

MATERIALS AND METHODS

This prospective study was conducted on 1,091 admitted adult patients in the dedicated malaria ward of an associated group of hospitals affiliated with S. P. Medical College, Bikaner, India, from September 2003 through December 2005. Detailed clinical, biochemical, and radiological examinations were conducted to establish the diagnosis of malaria and severe manifestations. Categorization of severe malaria and treatment by intravenous quinine was conducted according to World Health Organization (WHO) guidelines.²⁶ Formal approval of hospital ethical committee and written consent of patients were obtained for this study.

Selection criteria. Adult malaria patients with severe manifestations, evidence of *P. vivax* infection, and no evidence of *P. falciparum* infection by PBF, rapid diagnostic test (RDT), and PCR were included in the study.

Exclusion criteria. Patients who refused to give the written consent or had other concurrent illness or whose PCR examination showed evidence of *P. falciparum* mixed infections were not included in the study.

Diagnostic methods used to detect malaria parasites. Conventional thick and thin PBFs stained with Giemsa were examined under oil immersion (Figure 1). Slides were considered negative when there were no parasites in 100 high-power fields. The RDTs were based on detection of specific *Plasmodium* spp. lactate dehydrogenase (OptiMal test; Diamed AG, Cressier sur Morat, Switzerland) and histidine-rich protein 2 (Falcivax test; Zephyr Biomedical Systems, Goa, India). Evidence of *P. vivax* and absence of *P. falciparum* was further confirmed by PCR (Figure 2).

The PCR studies were targeted against the 18S ribosomal RNA gene of the parasite and used 1 genus-specific 5' primer and 2 species-specific 3' primers in the same reaction mixture. Some of the primer sequences were modified for this study:

1. 5'-ATCAGCTTTTGATGTTAGGGT ATT-3', genus specific;
2. 5'-TAACAAGGACTTCCAAGC-3', *P. vivax* specific; and
3. 5'-GCTCAAAGATACAAATATAAGC-3', *P. falciparum* specific. Each sample was subjected to a minimum of four rounds of PCR with various template amounts to eliminate overlooking *P. falciparum* co-infection.⁵

* Address correspondence to Dhanpat K. Kochar, Department of Medicine, S. P. Medical College, C-54, Sadul Ganj, Bikaner, Rajasthan 334003, India. E-mail: drdkkochar@yahoo.com

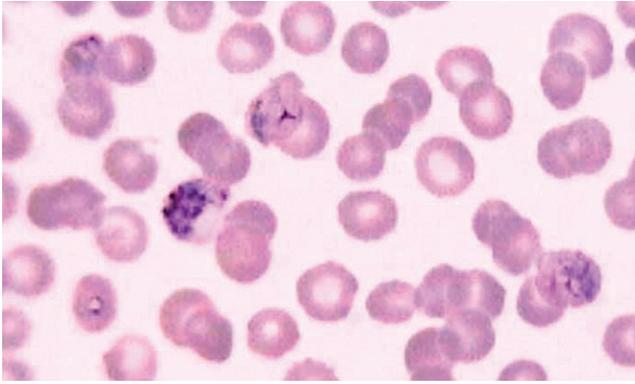


FIGURE 1. Peripheral blood smear (Giemsa stain, magnification $\times 1,000$) showing ring, trophozoite, and schizont stages of *Plasmodium vivax*. This figure appears in color at www.ajtmh.org.

Apart from PBF, RDT, and PCR, laboratory investigations included complete blood count, platelet count, bleeding time, clotting time, blood glucose, blood urea, serum creatinine, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, serum electrolytes, complete urine analysis, electrocardiogram, skiagram chest, and appropriate blood test to rule out typhoid fever, hepatitis B and C, leptospirosis, dengue, and infection with human immunodeficiency virus in all patients. Depending upon the clinical manifestations, other specific tests used included urine and blood culture, cerebrospinal fluid (CSF) examination, computed tomography (CT) of the head, ultrasonography of whole abdomen, and other relevant examinations.

RESULTS

A total of 1,091 patients with malaria were admitted during study period, of which 635 patients had *P. falciparum* and 456 patients had *P. vivax* malaria as diagnosed by PBF and RDT. Among those with severe manifestations as per WHO criteria, 40 patients (29 males and 11 females) had evidence of *P. vivax* infection and no evidence of *P. falciparum* infection by PCR (Table 1). The age of the patients ranged from 18 to

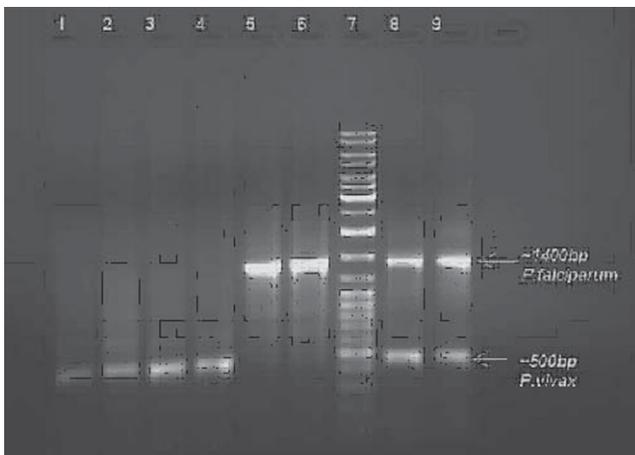


FIGURE 2. Polymerase chain reaction of samples tested. Lanes 1–4, *Plasmodium vivax* infection; lanes 5–6, *P. falciparum* infection; lane 7, 1 kb DNA ladder (SM#0331; Fermentas Inc., Glen Burnie, MD); lanes 8–9, mixed infection.

TABLE 1
Symptoms of patients with severe malaria positive for *Plasmodium vivax* by polymerase chain reaction

Symptom	No. (%) of patients (n = 40)
Jaundice (serum bilirubin > 3 mg%)	23 (57.50)
Renal failure (creatinine > 3 mg%)	18 (45)
Severe anemia (hemoglobin < 5 gm%)	13 (32.5)
Thrombocytopenia (platelet count < 100,000/mm ³)	9 (22.5)
Cerebral malaria (Glasgow coma score \leq 9/14)	5 (12.5)
Acute respiratory distress syndrome	4 (10)
Shock (systolic blood pressure < 80 mmHg)	3 (7.5)
Hypoglycemia (glucose < 40 mg%)	1 (2.5)
Multi-organ dysfunction (\leq 2 complications)	19 (47.5)

60 years (mean \pm SD = 29.65 \pm 11.72 years). The PBF showed predominantly trophozoites and the density of parasites was 8,400–60,000/mm³ (mean \pm SD = 19,665 \pm 9877.59/mm³).

Hepatic dysfunction and jaundice (Figure 3) was present in 23 (57.5%) patients and the mean \pm SD level of serum bilirubin was 4.31 \pm 3.52 mg% (maximum = 16.2 mg%) with predominant conjugated hyperbilirubinemia. Mean \pm SD level of AST was 111.25 \pm 97.47 IU/L (maximum = 426 IU/L), mean \pm SD level of ALT was 151.78 \pm 123.76 IU/L (maximum = 529 IU/L), and mean \pm SD level of alkaline phosphatase was 290.83 \pm 218.41 IU/L (maximum = 866 IU/L). To rule out viral hepatitis in these patients, a detailed serologic investigation that included IgM anti-hepatitis A virus antibody, hepatitis B surface antigen, IgM anti-hepatitis B core antibody, and IgM anti-hepatitis E virus antibody was conducted. Results were negative in all patients. Detailed ultrasonography was done to study the size and echo texture of the liver and gall bladder, intrahepatic or extra hepatic bile duct dilatation, and signs of portal hypertension.

Renal dysfunction was present in 18 patients (45%). Mean \pm SD blood urea level was 116.26 \pm 103.23 mg% (maximum = 252 mg/dL) and the mean \pm SD serum creatinine level was 3.85 \pm 3.24 mg% (maximum = 12.6 mg%). Other causes of renal dysfunction such as hypertension, diabetes mellitus, septicemia, hypotension, and shock were ruled out by appropriate investigations. Hemodialysis (2–8 dialysis in a patient) was required for six patients. Severe anemia was present in 13 (32.5%) patients, and the mean \pm SD hemoglobin level was 4.78 \pm 0.564 mg% (minimum = 3.5 mg%). Thrombocytopenia with a mean \pm SD platelet count 63,000 \pm 21,102.92/mm³ (minimum = 14,800/mm³) was observed in 5 (12.5%) patients,



FIGURE 3. Patient with jaundice. This figure appears in color at www.ajtmh.org.

of which 2 patients had severe epistaxis and required blood transfusions and platelet transfusions. Cerebral malaria (Figure 4) was present in five patients, of which two had associated seizures. A Glasgow coma score ≤ 5 was observed in two patients and a score of 6–9 was observed in three patients. Other causes of altered sensorium and seizures were ruled out by detailed CSF examination, CT scan of head, fundus examination, and serum electrolytes. Acute respiratory distress syndrome was seen in 4 (10%) patients. Details of combinations of severe manifestations are shown in Table 2. The commonest combination observed was the association of jaundice with renal failure. None of the female patients were pregnant or were in a puerperal period. Two patients died, of which one had ARDS, severe anemia, jaundice, and renal failure and another had ARDS, jaundice, and renal failure.

DISCUSSION

Severe and complicated malaria is usually caused by *P. falciparum* but it has been increasingly observed that *P. vivax* malaria, which was otherwise considered to be a benign malaria, with a low case-fatality ratio, can also occasionally result in severe disease as with *P. falciparum* malaria. The reported severe manifestations included cerebral malaria,



FIGURE 4. Patient with cerebral malaria. This figure appears in color at www.ajtmh.org.

TABLE 2

Spectrum of symptom combinations of severe manifestation in malaria patients*

Symptom	No. patients
CM, RF, SA, Thp	1
ARDS, RF, J, SA	1
RF, J, Thp	4
ARDS, J, SA	2
RF, J, SA	2
ARDS, RF, J	1
RF, J	2
RF, SA	2
CM, SA	2
J, SA	2

* CM = cerebral malaria; RF = renal failure; SA = severe anemia; Thp = thrombocytopenia; J = jaundice; ARDS = acute respiratory distress syndrome.

hepatic dysfunction, renal dysfunction, severe anemia, ARDS, shock, pulmonary edema, hemoglobinuria, and multiple organ involvement. These observations are largely based on a number of case reports worldwide and two recently reported large series from Papua New Guinea and Indonesia.^{27,28} However, most of these studies had some limitations. First, the co-morbid conditions including infections were not actively investigated. Second, microscopy was used for parasite detection and speciation, which routinely leads to underestimation and missing of mixed infections.^{4,7,9,11–13,18,20–22,24} There are few reports on severe malaria in which the diagnosis of *P. vivax* monoinfection was firmly established by PCR.^{3,5,8,10}

Complications in severe malaria are either sequestration related, such as cerebral malaria, renal dysfunction, hepatic dysfunction, and ARDS, or non-sequestration related, such as anemia and thrombocytopenia. Non-sequestration-related complications are known to occur in *P. vivax* infection quite frequently. However, for sequestration-related complications, it was always presumed that coexisting *P. falciparum* infection may evade appearance in blood film because of heavy sequestration.

In this prospective observational study, we report 40 patients with severe *P. vivax* malaria diagnosed by a protocol similar to a protocol previously reported.⁵ The most common complications observed were jaundice and hepatic dysfunction, which is similar to the reported observations in severe *P. falciparum* malaria and *P. vivax* malaria in this region.^{5,9,29–31} Renal failure, which was the second most common complication, has also been reported frequently in the Indian subcontinent.^{4,5,18} Cerebral malaria was observed in five patients; this has also been reported in one patient in Pakistan and in three patients in Bikaner, India.^{3,5} Status epilepticus has also been reported in India and Turkey.^{8,32} Other reported neurologic manifestations include acute inflammatory demyelinating polyneuropathy³³ and post-malaria neurologic syndrome causing bilateral facial paralysis.³⁴ Four patients had ARDS and two patients with these complications died. Pulmonary syndromes associated with *P. vivax* malaria include acute non-cardiogenic pulmonary edema, ARDS, acute pulmonary injury, and interstitial pneumonia.^{5,10–14} 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.²⁷ We observed severe anemia in 13 patients; this finding was the most commonly observed complication in a recent study from Indonesia.²⁸ Evidence of shock in one patient in this study was also reported in a patient

with *P. vivax* mono-infection detected by PCR.¹⁰ Multi-organ dysfunctions were recorded in 19 patients. Renal and hepatic dysfunctions were commonly seen together; however, ARDS had the worst prognosis. Similar observations were also recorded in previous studies.^{5,28}

Exact pathogenesis and organ-specific morbidity caused by *P. vivax* infection remains unrecognized and poorly studied because of a paucity of research in this area. *Plasmodium vivax* is widely believed to be incapable of causing cytoadherence and microvascular sequestration and therefore is unable to cause organ dysfunction. Recent observations have shown evidence of sequestration of parasites in lung vasculature during evaluation of lung injury in *P. vivax* malaria.³⁵ Cerebral dysfunction in *P. vivax* malaria may occur through generation of nitric oxide.³ Cytokines and leukotrienes may be responsible for severe anemia and hemostatic complications.³⁶ A report of *P. vivax* infection in pregnancy that resulted in low birth weight babies suggested sequestration of *P. vivax* in the placenta.³⁷ Recent microrheologic research that analyzed malaria severity in *P. vivax* infection clearly demonstrated enhanced aggregation, erythrocyte clumping, and reduced deformability affecting microcirculation.³⁸

If one considers the re-emergence of *P. vivax* malaria in several areas, our observations provide an impetus to study different issues related to severe *P. vivax* malaria. A further large-scale study is required to determine the underlying pathogenesis of severe disease and the degree to which it is related to multidrug resistance of *P. vivax* infection. There is also an urgent need to re-examine the clinical spectrum and burden of *P. vivax* malaria so that adequate control measures can be implemented against this emerging but neglected disease. The observation that a significant proportion of severe malaria morbidity is also caused by *P. vivax* would have tremendous implications for control of the infection especially as *P. vivax* invariably increases relative to *P. falciparum* under effective transmission reduction.^{39,40} Thus, every effort to reduce or eliminate malaria burden must also target *P. vivax* along with *P. falciparum* in regions where both of these species coexist.

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Authors' addresses: Dhanpat K. Kochar, Sanjay K. Kochar, Parmendra Sirohi, Abhishek Kochar, Mahesh P. Khatri, and Vikas Gupta, Department of Medicine, S. P. Medical College, Bikaner, Rajasthan, India. Ashish Das, Vishal Saxena, and Shilpi Garg, Birla Institute of Technology and Sciences, Pilani, Rajasthan, India.

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