Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading doi:

Spectrum of complications associated with *Plasmodium vivax* infection in a tertiary hospital in South-Western India

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ARTICLE INFO

Article history:
Received 1 September 2011
Received in revised form 15 September 2011
Accepted 15 October 2011
Available online 20 January 2012

Keywords:
Plasmodium vivax malaria
Complications
Benign tertian malaria

ABSTRACT

Objective: To determine the range and incidence of complications associated with *Plasmodium vivax* (*P. vivax*) malaria. **Methods:** A retrospective analysis was performed of all patients of *P. vivax* malaria admitted in Kasturba Medical College, Manipal between January and December, 2010. Patients with mixed malarial infection were excluded by appropriate tests. Clinical presentation and laboratory parameters were studied. **Results:** Medical records of 213 individuals who satisfied the inclusion criteria were reviewed. Anaemia was seen in 65 (30.5%), leucopenia in 38 (17.8%) and thrombocytopenia in 184 (86.4%) patients. Aspartate and alanine aminotransferases were elevated in 86 (40.4%), and 89 (41.9%) patients respectively. Hypoalbuminemia was observed in 157 (73.6%) cases. Elevated serum creatinine was noted in in 59 (27.5%) patients. Creatine kinase was elevated in 30 out of 59 patients (50.8%). Overall, 107 (50.2%) patients fulfilled WHO criteria for sever=e malaria. None of the patients succumbed to the disease. **Conclusion:** *P. vivax* malaria is a potentially severe disease, and the term "benign" tertian malaria is a misnomer. Despite significant morbidity, with timely and appropriate treatment *P. vivax* malaria has an excellent outcome.

1. Introduction

Plasmodium vivax (*P. vivax*) malaria, also known as benign tertian malaria, is a tropical disease with a global distribution. Once a dreaded infection, *P. vivax* malaria has now lost much of its notoriety, principally due to the widespread availability of powerful and efficacious antimalarial drugs. Moreover, the relatively greater severity of infection with *Plasmodium falciparum* (*P. falciparum*) has resulted in a shift of international policy and resources towards this more virulent form of malaria. While it is certainly true that *P. falciparum* is a source of significant morbidity and mortality, it is pertinent to note that a large fraction of the malarial burden outside of Sub-Saharan Africa remains attributable to *P. vivax*. The sheer burden of disease is astounding with annual global incidence estimated at 225 million[1]. The incidence in India is estimated at 1.5 million cases annually of which nearly 40% are due to *P. vivax*. In light of these statistics, we designed this study to focus on the various clinical and biochemical abnormalities associated with *P. vivax* malaria.

2. Materials and methods

2.1. Study settings

Kasturba Hospital, Manipal is a major tertiary care hospital in Southwestern India. For the purpose of this study, the catchment area of this hospital corresponds to the district of Udupi in which it is situated as well as the neighbouring districts of Uttara Kannada and Dakshina Kannada, with a combined population of approximately 4.36 million individuals.

A retrospective analysis of data of patients with *P. vivax* malaria admitted between January and December 2010 was conducted from medical records. All cases with mixed malarial infection *i.e.* both *P. vivax* and *P. falciparum* were excluded by means of peripheral blood smear examination and serological testing for histidine rich protein 2 by the Falcivax test (Zephyr Biomedical Systems, Goa, India). All patients included in the study had tested positive for *P. vivax* malarial parasite by either peripheral smear examination with Giemsa staining or fluorescein staining of buffy coat layer. Findings of clinical examination were recorded. Laboratory parameters including complete blood counts, renal and liver function tests, creatine kinase

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and blood glucose were collected. WHO criteria for severe malaria were used to identify patients with severe *P. vivax* malaria.

Primary outcome was defined as mortality due to infection with *P. vivax* malaria or complications thereof. Secondary outcomes included the various complications developed.

2.2. Statistical analysis

All data was analysed using SPSS Statistics version 17.0 (Chicago IL, USA). Continuous variables were presented as mean ± standard deviation (SD).

3. Results

213 patients who fulfilled the inclusion criteria were included in the study. Of them, 172 (80.8%) were males and 41 (19.2%) were females. Mean age was (33.17±14.85) years. Cases of malaria were seen throughout the year peaking between the months of May and August, corresponding to the Monsoon season (Figure 1).

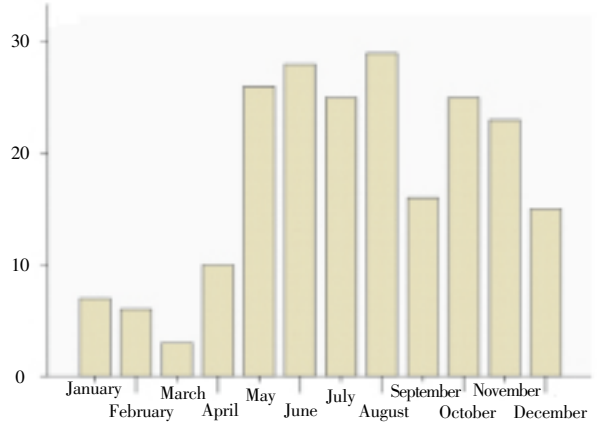

Figure 1. Monthly incidence of *P. vivax* malaria.

The principal presenting complaint was fever, which was present in all the cases. Two patients presented with hyperpyrexia. Seizures and altered sensorium were observed in three patients. Clinical examination showed hypotension in ten patients. Chest radiograms were suggestive of acute respiratory distress syndrome (ARDS) in four patients.

Analysis of complete blood counts revealed anaemia in 65 (30.5%) patients, leucopenia in 38 (17.8%) patients and thrombocytopenia in 184 (86.4%) patients. Liver function tests were also deranged; indirect hyperbilirubinemia was seen in 85 (39.91%) patients, direct hyperbilirubinemia was seen in 26 (12.21%). Malarial hepatitis was also observed, 86 (40.4%) patients had elevated serum aspartate aminotransferase levels, while 89 (41.9%) had elevated levels of serum alanine aminotransferase. Elevated alkaline phosphatase levels were noted in 40 (19%) patients. Hypoalbuminemia was seen in 157 (73.6%) patients while hypergammaglobulinemia was noted in 21 (10.1%) patients. Renal failure was encountered frequently; 44 (20.7%) patients had elevated blood urea levels, while serum creatinine was high in 59 (27.5%) patients. 27 (13%) patients had hypokalemia. 30 out of 59 (50.8%) patients had elevated serum creatine kinase levels.

These findings are summarized in Table 1. Patients were also scored according to the WHO criteria for severe malaria[2]. Neurological involvement in the form of seizures and coma were encountered in 3 (1.41%) patients, while severe anaemia (Hb < 5 g/dL) and renal failure (creatinine > 3 mg/dL) were seen in 1 (0.47%) and 2 (0.94%) patients respectively. Adult respiratory distress syndrome (ARDS) and shock were noted in 4 (1.88%) and 10 (4.69%) patients. Jaundice (serum bilirubin > 3.0 mg/dL), elevated liver enzymes (AST/ALT > 3 times upper limit of normal) and thrombocytopenia ($< 5\times10^4/mm^3$) were observed in 29 (13.62%), 13 (6.10%) and 68 (31.92%) patients respectively. Elevated muscle enzymes were noted in 30 of 59 (50.8%) patients in whom it was estimated. Hypoglycemia (Plasma glucose < 40 mg/dL), and disseminated intravascular coagulation were not encountered in any patients.

Overall, 107 (50.2%) patients were found to have severe malaria. Despite the frequency of complications observed, all patients included in the study survived. The primary outcome of mortality was therefore not seen in this study.

Table 1
Laboratory abnormalities encountered.

Parameter	Patients with deranged parameter (%)	Mean±SD
Haemoglobin	65 (30.50%)	12.92±2.24
Total leucocyte count	38 (17.80%)	6 019.25±2 493.17
Platelet count	184 (86.40%)	84 053.40±59 255.64
Indirect bilirubin	85 (39.91%)	–
Direct bilirubin	26 (12.21%)	1.15±2.61
AST[a]	86 (40.40%)	47.06±48.42
ALT[b]	89 (41.90%)	46.69±43.23
ALP[c]	40 (19.00%)	103.38±59.10
Albumin	157 (73.60%)	3.53±0.68
Globulin	21 (10.10%)	2.97±0.60
Blood urea	44 (20.70%)	34.68±23.94
Creatinine	59 (27.50%)	1.14±0.46
Potassium	27 (13.00%)	3.94±0.51
Creatine kinase	30/59 (50.80%)	196.44±247.593

a: AST=Aspartate aminotransferase; b: ALT=Alanine aminotransferase; c: ALP=Alkaline phosphatase.

4. Discussion

Although less virulent than *P. falciparum*, *P. vivax* can nevertheless produce severe complications[3]. The frequency of such complications as observed in our study is alarming, especially in the context of the massive global burden of *P. vivax* malaria. Within India, the estimated annual incidence of malaria is around 1.5 million cases, of which over 40% are due to *P. vivax*[1]. Moreover, over 80% of the Indian population is estimated to be at risk of infection with malaria.

In our study, thrombocytopenia was the commonest complication, seen in 184 (86.4%) patients. Severe thrombocytopenia below $20\times10^3/mm^3$ was observed in 17 (8.3%) patients; however, none of these patients displayed bleeding tendencies. In their study on *vivax* malaria, Sharma and Khanduri[4] reported thrombocytopenia in 96.4% patients with severe thrombocytopenia in 6% patients. Kochar *et al*[5] detected thrombocytopenia in 22.5% patients. Cases of severe thrombocytopenia have also been reported by Makkar *et al*[6] and Rodriguez *et al*[7]. Postulated mechanisms for thrombocytopenia include macrophage activation, increased levels of cytokines and antiplatelet immunoglobulin resulting in accelerated destruction of platelets. Other putative mechanisms include oxidative stress, sequestration in non-splenic areas and pseudothrombocytopenia due to clumping of platelets[8].

Deranged liver function tests were frequently noted in our study. 29 (13.62%) patients had serum bilirubin levels greater than 3 mg/dL and 13 (6.10%) had serum aminotransferases elevated over three times the upper limit of normal. Although, Sharma and Khanduri[4] detected these abnormalities in only 4% and 3.17% of patients respectively, they found higher levels of serum aminotransferases in individual patients, with aspartate aminotransferase and alanine aminotransferase values upto 1 901 U/L and 848 U/L respectively. Corresponding values noted in our study were 511 U/L and 434 U/L. In contrast, Kochar *et al*[5] reported hepatic dysfunction in 57.5% of their patients. Such cases of 'malarial hepatitis' are more typical of *P. falciparum*[9], but have occasionally been reported with *P. vivax*[10].

Renal failure was observed in 59 (27.5%) of our patients, although elevation of serum creatinine beyond 3 mg/dL was noted in only 2 (0.94%) patients. The highest level of serum creatinine seen was 3.9 mg/dL. *P. vivax* malaria has been reported in a number of studies[11-15] to be responsible for between 2.42% and 12.5% of all cases of malarial renal failure. Sharma and Khanduri[4] detected renal failure in 7% of their cases while Kochar *et al*[5] found renal failure in 45% of their patients.

Interestingly, the paediatric age group appears to be at a greater risk for renal failure following infection with *P. vivax*. Kaur *et al*[16] reported a paediatric case with uremic encephalopathy secondary to *P. vivax* induced renal failure. Haemolysis, volume depletion, disseminated intravascular coagulation, rhabdomyolysis[17], hyperbilirubinemia and heavy parasitemia[18] are among the various factors implicated in the pathogenesis of renal failure in malaria. Cytoadherence has also been suggested as a mechanism although its role appears to be only minimal[19].

Acute respiratory distress syndrome (ARDS) was seen in 4 (1.88%) patients in our study. Sharma and Khanduri[4] reported three cases of ARDS out of 221 patients with *P. vivax* malaria, while Kochar *et al*[5] noted ARDS in four cases out of 40 patients. Suggested mechanisms include small airway obstruction, impaired gas exchange, increased phagocytic activity and accumulation of pulmonary mononuclear cells[20]. Intriguingly, these underlying pathophysiologic processes appear to be independent of parasite sequestration within the pulmonary vasculature[21]. This point is borne out by the fact that patients with *P. vivax* malaria often develop ARDS after completing antimalarial therapy[22], suggesting an inflammatory rather than an infectious basis for this complication. In this context, the use of corticosteroid therapy in malarial ARDS remains controversial[23] although it has been used with some success in the treatment of another rare pulmonary complication of malaria-bronchiolitis obliterans organizing pneumonia.

Neurological involvement in the form of cerebral malaria is commonly encountered in *P. falciparum* malaria, but extremely unusual with *P. vivax*. Indeed only 42 cases have been reported in medical literature[24]. Kochar *et al*[5] diagnosed cerebral malaria in five cases. In our study, we found three patients with symptoms fitting into cerebral malaria including recurrent seizures in two cases and persistent confusion in one case. Numerous pathologic processes for cerebral malaria have been proposed including adherence of parasitized red cells to the cerebral vascular endothelium, fibrin microthrombi, agglutination of parasitized red cells and dysregulated local nitric oxide production. While *P. vivax* has traditionally been considered to be incapable of inducing cytoadherence, newer evidence suggests that such a phenomenon is indeed possible[25,26]. Similar to malarial renal failure, cerebral malaria with *P. vivax* occurs more often in the pediatric age group. Our patients were aged 14, 22 and 35 years. An important possibility to be ruled out in all such cases is that of mixed infection with *P. vivax* and *P. falciparum*. In all our three cases, tests for *P. falciparum* including both peripheral blood smear examination and serologic testing for falciparum antigen were negative, making such a possibility extremely unlikely[24].

Elevated serum creatine kinase levels are typical of *P. falciparum*[17], often in association with acute renal failure. Unexpectedly, elevated serum creatine kinase was seen in 30 out of 59 patients in whom it was done, including all the three cases of cerebral malaria, presumably as a result of seizures. The mean serum creatine kinase in these patients was (196.440±247.593) U/L, with a maximum level of 1 099 U/L; creatine kinase over 1 000 U/L was seen in two patients, both of whom had seizures. However, none of these patients developed classical rhabdomyolysis, as evidenced by myoglobinuria. While occasionally associated with *P. falciparum*, rhabdomyolysis is rare in *P. vivax* malaria. Siqueira *et al*[27] reported a case of *P. vivax* malaria with rhabdomyolysis; Poels *et al*[28] described rhabdomyolysis following *P. vivax* malaria in an individual with myoadenylate deaminase deficiency. TNF-α (myotoxin), red-cell sequestration in skeletal muscle, toxins derived from the parasite, and lactic acidosis have all been proposed as triggers for myositis, myonecrosis, and rhabdomyolysis.

Hypotension defined as a systolic blood pressure below 80 mmHg in adults and below 50 mmHg in children 1-5 years, was observed in 10 (4.69%) patients in our study. Kochar *et al*[5] noted hypotension in three cases. Proposed mechanisms for hypotension in malaria include metabolic acidosis, gastrointestinal bleeding, splenic rupture, dehydration and secondary bacterial septicemia. In our study, bacterial sepsis was ruled out by negative blood cultures in all the affected patients. Hypotension often carries a poor prognosis, in part due to pulmonary edema which can develop following rapid infusion of saline[29].

Severe anaemia below 5 g/dL was seen in only one patient; Kochar *et al*[5] also detected this complication in just one case. The relatively low parasite biomass of *P. vivax* indicates the presence of mechanisms beyond mechanical destruction of infected red cells alone. Malariotherapy studies have shown that for every infected erythrocyte destroyed during vivax infection, 32 noninfected erythrocytes are removed from the circulation compared to the loss of eight erythrocytes for every infected erythrocyte in falciparum malaria[30]. Cytokine-related dyserythropoiesis also probably contributes to anaemia[31].

Of note, certain complications known to occur with severe malarial infection were not seen at all in our study. These included hypoglycemia, hyperparasitemia and disseminated intravascular clotting, as evidenced by prolonged clotting times and the presence of schistocytes in peripheral blood smear. In contrast, complications like elevated muscle enzyme levels and hypoalbuminemia were seen frequently. Rare complications of *P. vivax* malaria such as cerebral malaria and ARDS were also encountered. The reason for this pattern of complications is not clear, and needs to be followed up in larger studies.

Of even greater significance was our finding that 107 (50.2%) patients fulfilled established criteria for severe malaria. This figure is especially daunting when factored with the magnitude of *P. vivax* malaria infection worldwide, and underscores the potentially massive morbidity this disease is capable of inflicting, and consequently the need to divert adequate resources towards combating this disease.

In summary, *P. vivax* malaria remains an important source of morbidity, albeit overshadowed by *P. falciparum*. Although infection with *P. vivax* was not associated with mortality, the high frequency of complications observed make the term "benign" tertian malaria a misnomer.

Conflict of interest statement

We declare that we have no conflict of interest.

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