The Study of Complications of Vivax Malaria in Comparison with Falciparum Malaria in Mumbai

Charulata S Limaye*, Vikram A Londhey**, ST Nabar***

Abstract

Introduction: Severe malaria due to P. vivax infection is increasingly observed now a days. Organ failure in vivax malaria is caused by mechanisms of inflammation as well as sequestration. In this study we have compared the complications in vivax malaria with those in falciparum or mixed malaria.

Aims and objectives: 1) To study various complications in adult inpatients of vivax malaria. 2) To compare the incidence of complications in vivax, falciparum and mixed malaria.

Materials and Methods: This was a retrospective observational study done at a tertiary care hospital in Mumbai over 3 months period. All adult indoor patients positive for malarial infection based on peripheral smear or malarial antigen (LDH) spot test were included in the study. Their demographic profile, complications, course in ward till discharge or death was noted. Data was analysed using appropriate statistical tests.

Results: 680 cases of malaria were included in the study. 338 were infected with P. vivax, 206 with P. falciparum, 136 with mixed infection. Severe disease was present in 162 (23.82%) cases of malaria of which 50 (31%) had vivax infection, 64 (39%) had falciparum infection and 48 (30%) had mixed infection. The complications seen in vivax malaria were: thrombocytopenia (68%), leukopenia (19%), ARDS (3%), high bilirubin (5%), acute renal failure (3.5%), anemia (3%), mucosal bleeding (8%), cerebral malaria (3.5%), hypotension (5%), metabolic acidosis (4%) and death (1.77%).

Conclusions: 31% cases of severe malaria had vivax monoinfection. Thrombocytopenia, leukopenia, acute respiratory distress syndrome, hypotension, mucosal bleeding were seen as frequently as in falciparum and mixed malaria. Acute renal failure, cerebral malaria, high bilirubin, anaemia, metabolic acidosis and death were also found in vivax malaria but less frequently than in falciparum and mixed malaria.

Introduction

Vivax malaria is long considered to have a benign course. It is known for multiple relapses; but the typical complications seen with falciparum malaria are not found with vivax monoinfection. However in the past few years there is a changing trend in the clinical manifestations of vivax malaria namely severe or complicated disease; sometimes even causing death.

The incidence of malaria in Mumbai is rising because of various factors like overpopulation, lack of cleanliness, construction works, water stagnation, migrant workers, insecticide resistance, and antimalarial drug resistance. Cases of malaria are seen throughout the year; but they peak during monsoon period (July-October). In our observation the mortality due to vivax malaria is rising since past two years whereas that due to falciparum infection has remained constant. In this study we compare various complications of vivax malaria with those of falciparum and falciparum-vivax coinfection (henceforth referred to as mixed malaria).

Materials and Methods

It was a retrospective observational study carried out at a tertiary care hospital in Mumbai. Study duration was three months of monsoon period (August- October of 2009). Institutional ethics committee approval was obtained. All adult patients admitted with acute onset fever and diagnosed as malaria based on positive peripheral smear examination or malarial antigen (LDH) spot test were included in the study. Following data was noted in each case: demographic profile, smear examination and/or antigen test, the species, complication(s), death or discharge from the hospital. All patients received treatment based on WHO recommendations for antimalarial chemotherapy. Complicated vivax malaria was treated like falciparum malaria using artemisinin based combination therapy (ACT). In statistical analysis the parametric data was analysed using unpaired t- test and nonparametric data was analysed by chi- square test with Yates correction.

Results

Total 680 cases of malaria were studied. 338 had P. vivax...
infection of which 202 had positive peripheral smear, 44 had positive antigen test and 92 had both tests positive. P. falciparum infection was found in 206 cases of which 94 had positive peripheral smear, 56 had positive antigen test, 56 were found positive by both methods. Mixed infection (falciparum and vivax coinfection) was found in 136 cases of which 124 had both species positive on the peripheral smear; and 12 cases had the peripheral smear positive for vivax infection and antigen test positive for falciparum infection. Median age of patients of vivax malaria was 29 years, of falciparum malaria was 30.5 years and of mixed malaria was 31.5 years with no statistically significant difference. The number of patients infected with different species of malaria is given in Figure 1.

Severe disease was present in 162 (23.82%) cases; including 50 (14.79%) vivax, 64 (31.07%) falciparum and 48 (35.30%) mixed malaria. Severe malaria was classified as per WHO 2000 definition.1

Thirty one percent of severe malaria cases had vivax monoinfection; 39% had falciparum monoinfection; and 30% had mixed infection. Parasitic index was available in 20 cases of severe vivax malaria and mean parasitic index was 1.2%.

The relative frequencies of serious complications in vivax, falciparum and mixed malaria are shown in Figure 2.

Thrombocytopenia (platelet count<1,00,000/cmm) was observed in 68% cases of vivax and 73% cases each of falciparum and mixed infection. The difference was not statistically significant. (p=0.9). All patients had a rise in platelet count after treatment. Median 3.5 days were required for normalisation of platelet count after starting therapy. Mucosal bleeding and petechial rash was observed in 8.8% cases of vivax malaria with no significant difference from falciparum and mixed malaria. Life-threatening major hemorrhage was not seen in vivax.

Total leucocyte count was low (<4000/cmm) in 66 (19.53%) cases of vivax, 38 (18.45%) of falciparum and 26 (19.12%) of mixed malaria. Leucocyte count increased to normal after therapy.

Severe anemia (Hb<5gm/dL) was significantly (p=0.03) more common in falciparum 26 (12.62%) and mixed 16 (11.76%) than in vivax infection 10 (2.96%). The need for packed red cell transfusion was more in falciparum 24 (11.65%) and mixed 16 (11.76%) than vivax malaria 8 (2.37%).

Acute renal failure (creatinine>3mg/dL) was significantly (p=0.001) more common in falciparum 40 (19.42%) and mixed 18 (13.23%) than vivax 12 (3.55%). Four patients of vivax malaria required hemodialysis whereas 26 patients of falciparum (12.62%) and 14 patients of mixed malaria (10.29%) were dialysed.

ARDS (PaO2/FiO2<200, diffuse pulmonary infiltrates, normal left atrial pressure) was seen in 10 (3%), 16 (7.7%), 12 (8.8%) cases of vivax, falciparum, mixed malaria respectively. The difference between occurrences of ARDS among the three groups was not statistically significant (p=0.34).

Cerebral malaria (coma/multiple convulsions) was less common in vivax infection 12 (3.55%) than falciparum 28 (13.19%) and mixed 22 (16.18%) infection. (p=0.01).

Hypotension on presentation (systolic BP<70 mmHg) was equally prevalent in all three groups (5.32% in vivax, 4.85% in falciparum, 5.88% in mixed). Metabolic acidosis was more frequent in falciparum and mixed malaria than vivax malaria.

Incidence of high bilirubin (>3mg/dL) was significantly higher (p<0.01) in falciparum 46 (22.33%) and mixed malaria 54 (39.7%) than vivax malaria 18 (5.32%). The mean bilirubin concentration among the patients with hyperbilirubinemia in vivax group was 7.02±1.49 mg/dL, in falciparum group was 18.89±2.90 mg/dL, in mixed group was 13.73±2.70 mg/dL.

Mortality was significantly lower (p=0.03) in vivax malaria (6 cases: 1.77%) than in falciparum (20 cases: 9.71%) and mixed malaria (14 cases: 10.29%). ARDS was the most common life threatening complication of vivax malaria. All 6 deaths were due to ARDS. Four cases of these also had renal failure and 2 of them required dialysis. These 2 cases had cerebral involvement as well. We analysed the 40 cases of malaria deaths. Five were symptomatic for <3 days before being referred to our centre; 18 were symptomatic for 3-6 days and 17 were symptomatic for >6 days before coming to us. Many had received antimalarial treatment before coming to us but the details were not available.

Discussion

Vivax malaria was always described as a benign disease. However in the past few years many cases of severe vivax malaria were seen and some cases resulted in death. Hence this study was done to find out various complications of vivax malaria and to compare them with those of falciparum and mixed malaria. The exact causes of changes in the clinical profile of vivax malaria are uncertain. They may include genetic alterations of the parasite or change in vector and its biting habits or chloroquine resistance or increasing use of ACTs. Further research is needed to answer these questions.

It was previously presumed that the severe disease with vivax infection is actually caused by coinfection of vivax and falciparum species. Schizonts of P. vivax are detected in venous blood whereas those of P. falciparum remain undetected as they are present in the capillaries of internal organs. However with application of the recently developed tests of malarial antigen and the nucleic acid amplification technique it has become evident that vivax monoinfection can be a cause of severe malaria and death. The malarial antigen spot test using parasite LDH which is widely available and PCR test which is used mainly for the academic purpose can differentiate between vivax monoinfection and falciparum infection. In 2009 Kocher et al reported series of 11 cases of severe vivax malaria from Bikaner.3 They used antigen and PCR test to exclude falciparum co-infection.

The mechanisms of organ involvement in vivax malaria are debatable. Enhanced inflammatory responses as well as the sequestration of parasitized red cells in microcirculation were thought to be the possible mechanisms. Andrade et al found a strong linear trend between increased levels of C-reactive protein, TNF-alpha, IFN-gamma, IFN-gamma/IL-10 ratio and the disease severity of vivax malaria. Price et al reported that the plasma concentrations of TNF-alpha are higher in vivax as compared to falciparum malaria with similar degree of parasitemia. In all cases of ARDS with vivax malaria reported so far, the symptoms developed after starting antimalarial therapy; raising the possibility of pulmonary inflammatory response to parasite killing. Thus the inflammatory and immunological
response plays a significant role in pathophysiology of severe vivax malaria. In the study by Andrade et al in Brazil the patients with severe vivax malaria were younger, had lived in the endemic area for shorter time and had less previous episodes of malaria.5

In our study the incidence of ARDS/ALI, thrombocytopenia, leucopenia, mucosal bleeding, hypotension was as high as in falciparum or mixed malaria. (No statistically significant difference was noted in the incidences.) Other complications seen in vivax malaria less frequently than falciparum and mixed malaria were cerebral malaria, acute renal failure, hyperbilirubinemia, anaemia and metabolic acidosis. The complications of vivax malaria observed by Sharma et al in a study from Delhi2 were thrombocytopenia, hepatic dysfunction, renal failure, ARDS and hemolysis. Tjitra et al found anaemia, ARDS, cerebral malaria as major complications of vivax malaria in Papua, Indonesia. Severe anemia and respiratory distress were also noted as complications of vivax malaria by Genton et al and Picot et al.10 The incidence of severe disease among inpatients of malaria in our study was similar to that found by Tjitra et al.4

Many cases of severe thrombocytopenia caused by vivax malaria have been reported in literature.11,15 However in our study life-threatening haemorrhage was not observed in any patient. The platelet count increased with the treatment of vivax malaria as also reported by Jadhav et al.16 Immune mediated response to a given parasite burden in vivax than in falciparum demonstrated progressive alveolar capillary dysfunction after treatment of vivax malaria suggesting a greater inflammatory imbalance.31 Two out of 6 patients with severe vivax malaria had ARDS should be kept in mind by the clinicians as it is life threatening and timely intervention can be life saving. The deaths that occurred due to P. vivax infection were with ARDS, the onset of which was usually after starting antimalarial treatment. In our hospital based study the incidence of complications may be higher than the incidence in community; and is a limitation of the study. Severe vivax malaria is a relatively new clinical entity and further studies from different parts of India are needed.

References


