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SPECTRUM OF CLINICOPATHOLOGICAL AND BIOCHEMICAL VARIATIONS AMONG SEVERE PLASMODIUM VIVAX MALARIA CASES: A VISION FROM EASTERN INDIA

Dr. Tanushree Mondal[1], Dr. Saumen Nandi[2], Dr. Badal Kumar Sahu[3], Dr. Anindya Mukherjee[4]

1. MD, Associate professor, Dept of Community Medicine, Medical college, Kolkata
2. MD, DM, Assistant Professor, Department of Chest Medicine, Nil Ratan Sircar Medical College Kolkata
3. MBBS, Post Graduate Trainee, Department of Internal Medicine, Burdwan Medical College Burdwan.
4. MD, DM, Senior Resident, Department of Cardiology, Nil Ratan Sircar Medical College, Kolkata

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ABSTRACT

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Background: Plasmodium vivax (P. vivax) is geographically widely distributed with up to 2.5 billion people at risk and an estimated 70-80 million cases every year. India contributes 77% of the total malaria in Southeast Asia. Retrospective analysis of burden of malaria showed that disability adjusted life years due to malaria were 1.86 million years. According to recent study West Bengal contributes 11% of total malaria cases in country.

Aim and objective: This study tends to focus on severe and non-severe vivax malaria, the complications and outcome of P. vivax malaria infections as there is very limited information on age- and sex-specific seasonal prevalence of malaria in different paradigms in the country with most of the point prevalence studies in India have been carried out for outbreak/epidemic investigations.

Materials and Methods: A hospital based prospective study was conducted over a period of one and half years in medical college and hospital comprising of 138patients with fever (≥37.5˚C), peripheral smear and/or rapid diagnostic tests positive for P. vivax. Previously established cases of CKD, hematological abnormalities, chronic liver diseases, neuro-psychiatric disorders were excluded from our study. Demographical, clinical and laboratory parameters including liver function test, renal function test were documented and were presented in tabular, graphical and statistical means.

Observation and Results: 138 hundred patients were taken up for the study, which included males and females. Majority of the patients were in the second decade. Jaundice was present in 22% of patients and

vomiting in 32% of the patients. Hepatomegaly was seen in 16 % cases and 33% cases had splenomegaly. ARDS was seen in 16% of severe malaria cases. Acute kidney injury was seen in 8% and cerebral malaria was seen in 12 % of severe malaria cases. Multi organ dysfunction was seen in12 % cases. There was 1 death in the study due to multi organ dysfunction.

Conclusion: Life threatening complications such as ARDS, AKI, cerebral malaria and MODS can be seen in P. vivax mono infections.

Corresponding author*
Dr Anindya Mukherjee

INTRODUCTION

William Osler said that ―Humanity has but 3 great enemies; fever, famine, and war; of these by far the greatest, by far the most terrible is fever. Malaria has plagued mankind since long. For centuries it prevented any economic development in vast regions of the world. It continues to be a huge social, economic and health problem in many parts of the world. Incidence of malaria worldwide is estimated to be 300-500 million clinical cases per year causing more than one to three million deaths every year. [1]

Malaria is a febrile illness transmitted by infected female anopheles mosquito and caused by protozoa of genus plasmodium. Four species of the Plasmodium cause nearly all malarial infections in humans. These are Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae. Plasmodium knowlesi, a fifth species previously confined to monkeys, is now implicated in human disease.[2]

Malaria continues to be one of the major public health problems of India with around 1.5 to 2million confirmed cases per year with approximately 1000 reported malarial deaths every year, but according to WHO, SEARO, this figure could be 20 million cases with 15000-20000deaths annually.[2] Among South East Asia region India shares two thirds of burden (66%).[3]P. vivax contributes to >40% and P. malariae and P. ovale contributing to <10% of theburden.[2]

P. vivax threatens almost 40% of the world's population causing an estimated 400 million clinical infections each year representing the widest spread plasmodium species.[4]Studiesfrom India, Indonesia, Papua New Guinea and Thailand have shown that 21-27 % patients with severe malaria had P. vivax mono infection. Overall mortality is around 0.8-1.6%.[5]Almost half of the1.6 million confirmed cases in India in the year 2010 were caused by P. vivax, illustrating that vivax remains a major public health issue in the country. 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.[4]

Recent studies have shown that complications associated with P. vivax are on the rise and outcomes are similar to that of P. falciparum malaria.[5] The trend of disease with P. vivax malaria is changing globally. It is increasingly recognized that serious and life threatening complications can occur with P. vivax malaria due to evolution of P. vivax or due to some unexplored host factors or both.[6]The decrease in the incidence of P. falciparum is, on average, more than that of P. vivax, suggesting that P. vivax responds more slowly to control measures, possibly because of its biological characteristics.[7] Hence a study on the complications of P. vivax malaria and comparative analysis of in patients with severe and non-severe P. vivax malaria would help to gather information on the morbidity caused by the disease and may help to reduce the burden and unexpected mortality due to the disease.

MATERIALS AND METHODS:

This study was a prospective study done over a period of one and half years from January 2013 to July 2014. Data were collected from patients of age more than 18 years and less than 60 years who attended Medical college hospital having fever (≥37.5˚C) and peripheral smear and/or Rapid diagnostic test positive for P. vivax. A total of 138 patients, meeting the selection criteria, were selected using purposive sampling techniques. They were followed from admission till recovery, discharge or death whichever was earlier.

Patients with P. falciparum, P. ovale, P. malariae co-infection, age less than 18 years and more than 60 years, pregnant female patient of any age group, previously established cases of chronic kidney disease, previously established case of hematological abnormalities, previously established case of chronic liver disease, previously established case of neuropsychiatric disorders were excluded from the study.

Following investigations were done in all cases:Haemoglobin estimation by cyan-methemoglobin method, Total and differential leukocyte count, Platelet count, ESR estimation by Westergren method, Peripheral smear for malaria parasite-both thick and thin smears stained with JSB stain and seen under oil immersion and Rapid diagnostic test(immune-chromatographic) for P. vivax, Histidine rich protein-2 test to rule out P. falciparum, Random blood sugar, Urine analysis, Liver function test – Total and Direct Bilirubin, SGOT, SGPT, S. protein and S. albumin, Renal function test – S. urea and S. creatinine, Coagulation profile – Bleeding time, Clotting time, activated partial thromboplastin time, Prothrombin time. In selected cases, chest x ray, blood culture, cerebrospinal fluid analysis, and arterial blood gas analysis were done.

Data collected was analyzed by frequency, percentage, mean, standard deviation and chi-square test. Once the patient was diagnosed to have malaria, they were started on anti-malarial drugs according to the new WHO guidelines for treatment of malaria. Other supportive treatment was given according to the patient's condition.

RESULTS & ANALYSIS

138 cases of P. vivax malaria were studied, out of which 25 were classified to be severe vivax malaria on the basis of WHO criteria. Out of those 25 cases of severe P. vivax malaria, 16 were male and 9 were female. Majority of the patients were in the age group of 21-30years and 31-40 years. When mean age of distribution of severe vivax malaria was compared with the same of non-severe vivax malaria showed no significant difference. Table 1 shows the comparison of symptoms & signs between severe & non-severe vivax malaria. Fever, jaundice and vomiting were the three most common symptoms. Fever was the commonest symptom in both severe and non-severe malaria. 96% of patients with severe vivax malaria presented with fever whereas 93% of non-severe vivax malaria presented with fever. 28% of patients with severe vivax malaria and 8% of patients with non-severe vivax malaria had hyperpyrexia. The association of fever between severe and non-severe vivax was not statistically significant; but when hyperpyrexia is taken into consideration separately, the association of hyperpyrexia was found statistically significant with cases of severe vivax malaria (Table 2).Altered sensorium was present in 12% of the patients with severe vivax malaria. Altered sensorium included patients with patients with GCS≤ 10. The association was statistically significant with altered sensorium present in severe vivax cases only. Jaundice was presenting complaint in 52% of severe vivax and 16% of non-severe malaria. The association was statistically significant with jaundice being common in severe vivax malaria ($p < 0.001$). Petechiae were seen in 12% of patients with severe plasmodium vivax malaria and 6% of patients with non-severe vivax malaria. Petechiae did not show any significant association with severe and non-severe vivax malaria ($p = 0.311$). Oliguria was seen in 8% of patients with severe vivax malaria. Oliguria is defined

as urinary output between 100-400 ml/day. Oliguria showed significant association with vivax malaria (p= 0.027).

Pallor was seen in 32% of the patients with severe vivax malaria and 20% of patients with non-severe vivax malaria. Icterus was seen in 52% of patients with severe vivax malaria and 16% of patients with non-severe vivax malaria. Splenomegaly was present in 56% patients with severe vivax malaria and 30% of patients with non-severe vivax malaria. Respiratory system involvement was seen in 16% of patients with severe vivax malaria. Respiratory manifestation included bronchitis, rhonchi, crepitation and ARDS. Central nervous system abnormality was seen in 12% of patients with severe plasmodium vivax malaria.

Out of 13 patients with icterus 5 patients had bilirubin <3 mg% with 4 patients having unconjugated hyperbilirubinaemia.8 patients had bilirubin >3 mg% with 7 patients having conjugated hyperbilirubinemia. The association of ALT with bilirubin is significant with ALT level increasing with increasing bilirubin level (χ^2=6.099, p= 0.0474). Majority of patients with severe vivax malaria had hemoglobin (Hb) levels between 8-10.9 gm% and greater than 11gm%. 3 Patients had Hb level less than 5 gm%. There is significant association between anemia and splenomegaly in severe vivax (χ2 =4.573, p= 0.0325). There is significant association between severe thrombocytopenia and severe vivax malaria (χ^2=59.546, p<0.001).Out of 138 plasmodium vivax malaria patients studied 56% had thrombocytopenia. 12(8%) patients had severe thrombocytopenia (<50,000 cells/cu mm) and 66(47%) patients had platelets between 50,000-1, 00,000 cells/cu mm. The association between thrombocytopenia and splenomegaly is significant (χ^2=8.492, p= 0.0036).

Significant correlation between hemoglobin level and platelets was seen. In severe malaria both platelet and hemoglobin is decreased (p= 0.0191). Majority of patients had normal leukocyte count in our study. Leukocytosis with total leukocyte count greater than 12000 cells/cu mm was seen in 4% of patients. All patients with leukocytosis had raised neutrophil count indicating superadded bacterial infection. Leukopenia with total leukocyte count below 4000 was seen in 5% of patients. 91%of 138 patients had leukocyte count within normal limits and similar results. Majority of patients had leukocyte count between 4000-12000 cells/cu mm. 5% of patients had lymphopenia with leukocyte count below 4000 cells/cu mm. 12% of patients with severe vivax malaria had multiple system involvement with CNS, respiratory system and hepatobiliary system involvement together.

Severe vivax malaria patient received ACT, whereas non severe vivax malaria received chloroquine and primaquine.

One patient with severe plasmodium vivax expired out of 138 patients studied. He had multi system dysfunction in form of deranged hepatic function, deranged hematological parameters in form of thrombocytopenia, acute renal failure and central nervous system involvement.

Patients with Hb<7 gm% had longer stay in hospital and required blood transfusion and other measures to make them hemodynamically stable. 83% of the patients' duration of hospital stay was less than 7 days. 1 patient expired on 4th day due to multi-organ failure.

DISCUSSION

Malaria is a parasitic infection of global importance and is a major health problem in India as well as West Bengal state, accounting for sizeable mortality, morbidity and economic loss.

Malaria is a multi-system disease, present study was done to evaluate clinical and biochemical profile of severe plasmodium vivax malaria. The present study was conducted in medical college and hospital, Kolkata where malaria incidence is high. According to WHO criteria laid down to identify severe malaria out of 138 consecutive P. vivax malaria patients studied, 25 were identified to be severe according to clinical and biochemical parameters. In a study conducted by Farogh et al maximum number

of patients belonged to age group 21 -30 years.[8] According to the study of Muddaiah M and Prakash maximum number of patients were in between age group 21-30.[9] In a study conducted by Bashawri LAM et al the mean age group was 25.34±14.34 years.[10]

The working group is the age group which is predominately affected, because this is the group which is exposed to mosquito bites especially in fields and outdoor. The study follows the age pyramid of our country; the base of age pyramid is formed by young people and apex by older age group which constitute lesser percentage of population. In the present study, the maximum numbers of patients (32%) were in the group of 21-30years.

In the study conducted by Bashawri LAM et al the ratio of male to female patients was 3.15:1 and according to Jadhav UM et al, 915 patients were male and 650 patients were female the ratio being 1.40:1.[10,11] Males are more frequently exposed to the risk of acquiring malaria than females because of the outdoor life they lead. Further, females in India are usually are better clothed than males.

In our present study, the total number of males outnumbered females with the ratio of 2.06:1. In the study by Muddaiah M and Prakash PS from Mangalore, symptom analysis showed that all cases had fever (100%), nausea and vomiting in 37.36% of cases, headache in 33.6%of cases, jaundice in 15.78% cases, cough in 11.57% cases, pain abdomen in 5.78% cases and altered level of consciousness in 4.21% of cases.[9]

In our study fever was the commonest symptom in both severe and non-severe malaria. 96% of patients with severe vivax malaria presented with fever whereas 93% of non-severe vivax malaria presented with fever. 28% of patients with severe vivax malaria and 8% of patients with non-severe vivax malaria had hyperpyrexia.

Nausea and vomiting was seen in 36% of severe plasmodium vivax malaria and 31% of non-severe vivax malaria. Pain abdomen was presenting complaint in 16 % of severe malaria and 12% of non-severe vivax malaria. Headache was seen in 28% of severe plasmodium vivax malaria and 23% of non-severe vivax malaria. Breathlessness was seen in 8 % patients with severe vivax malaria. Altered sensorial was present in 12% of the patients with severe vivax malaria. Jaundice was presenting complaint in 52% of severe vivax and 16% of non-severe malaria. Petechiae were seen in 12% of patients with severe plasmodium vivax malaria and 6% of patients with non-severe vivax malaria. Oliguria was seen in 8% of patients with severe vivax malaria. Altered sensorium and breathlessness were seen in severe vivax malaria cases only. Thus fever, jaundice, vomiting, headache and pain abdomen were commonest presenting symptom of vivax malaria. Even though malaria is commonly associated with thrombocytopenia, rash and petechial haemorrhages in the skin or mucous membranes are not the common presentation features.

Pallor was seen in 32% of the patients with severe vivax malaria and 20% of patients with non-severe vivax malaria. Icterus was seen in 52% of patients with severe vivax malaria and 16% of patients with non-severe vivax malaria. Splenomegaly was present in 56% patients with severe vivax malaria and 30% of patients with non-severe vivax malaria. Respiratory system involvement was seen in 16% of patients with severe vivax malaria. Central nervous system involvement was seen in 12% of patients with severe plasmodium vivax malaria. Variations in different studies may be due to some studies having concentrated only on malarial hepatitis and jaundice in malaria and others on haematological parameters only. In India, about 70% of the infections reported are due to P. vivax; 25-30% due to P. falciparum and 4-8% are due to mixed infections. P. malariae is responsible for less than 1% of infections in India.

Anaemia is a common manifestation of malaria. In our Study it was present in 60% of patients with severe vivax malaria. Among 25 patients of severe vivax malaria 2 had haemoglobin level below 5g/dl. WHO criteria

classify severe malaria as haemoglobin level below 5 mg/dl but 3 patients who were severe malaria based on other criteria had Hb level between 5-8 mg/dl.

Out of 15 anaemia patients, 11 patients had splenomegaly, this indicates that other factors other than splenic sequestration lead to anaemia. It is known that in heavily endemic malaria areas, it is almost inevitable that malaria infection will be associated with anaemia, although malaria may not be the prime cause of it. Out of 138 plasmodium vivax malaria patients studied 56% had thrombocytopenia. 12(8%) patients had severe thrombocytopenia (<50,000 cells/cu mm) and 66(47%) patients had platelets between 50,000-1, 00,000 cells/cu mm. In our study 43% of patients with thrombocytopenia had splenomegaly, indicating that splenic sequestration is not the only mechanism for thrombocytopenia and other causes like immune mediated lysis and dyspoietic process in marrow may be responsible. Majority of patients had normal leucocyte count in our study. Leukocytosis with total leukocyte count greater than 12000 cells/cu mm was seen in 4% of patients. All patients with leukocytosis had raised neutrophil count indicating superadded bacterial infection. Leukopenia with total leukocyte count below 4000 was seen in 5% of patients. 91% of 138 patients had leukocyte count within normal limits and similar results were observed by Bashawri LAM et al in their study.[10] Jaundice was seen in 52% of patients with severe plasmodium vivax malaria and 16% with non-severe vivax malaria. 13 patients with severe vivax malaria had icterus. Among these 5 patients had bilirubin< 3 mg% and majority had unconjugated hyperbilirubinemia and 8 patients had bilirubin ≥ 3% out of which majority had conjugated hyperbilirubinemia. Haemolysis alone can never cause severe jaundice or predominantly conjugated hyperbilirubinemia along with raised liver enzymes. Hence hepatocellular damage by malaria parasite may be the proposed cause for deranged liver parameters. Total serum protein and albumin/ globulin ratio in this study were all within normal range signifying absence of chronic liver dysfunction. The acuteness of hepatic dysfunction was probably too short for manifestation of impaired synthesis of serum proteins by the liver, if any.

Renal failure in the form of acute renal failure was noted in 2 patients with severe vivax malaria (8%).

Death was seen in 1 patient of severe vivax malaria patients. Death was due to multi organ dysfunction. He had deranged hepatic, haematological and renal parameters. Death was not seen in any patient in the non-severe vivax group. All 25 patients classified under severe vivax malaria were treated with ACT (artemesinin combination therapy) and rest of 113 patients were treated with chloroquine and primaquine.

This study focuses on the severe vivax malaria cases which despite being so prevalent and widely distributed remains overshadowed by falciparum malaria. Only P. vivax mono-infection cases were considered; even mixed infection cases were excluded. Previously diagnosed cases of chronic kidney diseases, chronic liver disease, neuropsychiatric patients and patients with haematological abnormalities were excluded from the study so as to elicit the effect of P. vivax effects on various systems of human body. Patients greater than 60 years were excluded from the disease since elderly patients might have pre-existing haematological, kidney and liver problems which might add as confounding factors.

There is also limitation in our study. This is a hospital based prospective study. The sample size should be bigger and population based studies should be done. The follow up period was only 4 weeks which need to be longer to include cases of relapse and resistant cases of P. vivax.

CONCLUSION

This study highlights the fact that P. vivax malaria, though traditionally considered to be a benign entity, can also have a severe and complicated course which we usually associate with P. 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.

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Table 1: Comparison of symptoms & signs between severe & non-severe vivax malaria

Parameters	Sub-parameters	Severe vivax malaria (n=25)	Non-severe vivax malaria (n=113)	Chi-square value (d.f.)	p-value
Symptoms	Fever	22(88.0%)	99(87.6%)	0.003 (1)	0.957
	Vomiting	9(36.0%)	36(31.9%)	0.1160 (1)	0.689
	Pain abdomen	4(16.0%)	14(12.4%)	0.235 (1)	0.628
	Headache	7(28.0%)	27(23.9%)	0.186 (1)	0.666
	Breathlessness	3(12.0%)	0 (0.0%)	13.861 (1)	<0.001*
	Altered sensorium	3(12.0%)	0 (0.0%)	13.861 (1)	<0.001*
	Bleeding	4 (16.0%)	0 (0.0%)	18.620 (1)	<0.001*
	Jaundice	13(52.0%)	18(15.9%)	15.292 (1)	<0.001*
	Petechiae	3(12.0%)	7(6.2%)	1.026 (1)	0.311
	Oliguria	2(8.0%)	1(0.9%)	4.873 (1)	0.027*
Signs	Pallor	8(32.0%)	23(20.4%)	1.594 (1)	0.207
	Icterus	13 (52.0%)	18 (15.9%)	15.292 (1)	<0.001*
	Splenomegaly	15 (60.0%)	31(27.4%)	9.770 (1)	0.002*

	Hepatomegaly	8(32.0%)	15(13.3%)	5.168 (1)	0.023*
	Respiratory signs	4(16.0%)	0 (0.0%)	18.620 (1)	<0.001*
	CNS manifestation	3(12.0%)	0 (0.0%)	13.861 (1)	<0.001*

*Significant

Table 2: Distribution of fever in vivax patients

Fever	**Grade of fever**	**Non-severe malaria**	**Severe malaria**	**Chi-square value (d.f.)**	**p-value**
Fever in vivax patients	Hyperpyrexia	9(8.0%)	7 (28.0%)	8.128 (2)	0.017
	Fever	90 (79.6%)	15 (60.0%)		
	Afebrile	14 (12.4%)	3 (12.0%)		