

Profile of Liver Dysfunction in Plasmodium Vivax Malaria

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ABSTRACT

Introduction: Malaria due to *P. vivax* infection increased now days. *Vivax* malaria causes organ failure by inflammation and sequestration. *P. vivax* mono-infection could also result in multiple organ dysfunction and severe life-threatening disease as seen in *P. falciparum* infection. Study aimed to describe the various clinical manifestations and biochemical parameter for liver dysfunction in association with *P. vivax* malaria.

Material and methods: This prospective observational study was carried out at Sarojini Naidu Medical College, Agra. It included all the cases presented with fever with evidence of jaundice. Diagnosis of malaria was confirmed by both thick and thin blood film stained with Leishman's stain for malarial parasite and M. P. Elisa. Detailed history, clinical examination, biochemical parameter for liver function was done in all patients.

Results: 200 *P. vivax* positive cases were included in the study (96 males and 104 females) out of which 54 (27%) patients have serum bilirubin >3mg/dl (48 patients, serum bilirubin 3-10mg% and 6 patients with >10 mg%). Out of 54 patients having serum bilirubin >3mg/dl, 33 patients had more increase in indirect bilirubin and 21 patients had more increase in direct bilirubin. SGOT 40-120IU/L was present in 99 cases and >120IU/L was present in 42 patients. SGPT 40-120IU/L was present in 99 cases and >120IU/L was present in 12 cases.

Conclusion: Severe *vivax* malaria now very common with increasing liver dysfunctions which is more common in young people evident by the level of serum bilirubin and liver enzymes.

Keywords: *Plasmodium vivax*, liver dysfunction, direct and indirect serum bilirubin

INTRODUCTION

Malaria is a common public health concern in tropical countries, according to the world malaria report 2010, there were 225 million case of malaria and estimated 781000 deaths worldwide in 2009.¹ Almost all complications and death from malaria are caused by *P. falciparum*.² Recently a changing trend is observed not only in the clinical manifestations but also in the pattern of complications in malaria.

Cerebral malaria was the predominant manifestation of severe malaria over a decade ago, whereas now days the combination of jaundice and renal failure is more common.³ Although *P. vivax* malaria has an enormous burden of disease, research is grossly inadequate because *P. vivax* malaria supposed to be cause only benign tertian fever and an uncomplicated cause of illness. Now a days, it has become evident that *P. vivax* mono-infection also be involved in multiple organ dysfunction and severe life threatening disease as seen in *P. falciparum*.^{4,5}

There are many report of plasmodium vivax malaria leading

to complication include cerebral malaria with generalized convulsions and status epilepticus.⁶ Severe anemia^{7,8} hepatic dysfunction and jaundice⁷⁻¹⁰, and acute renal failure^{7,8} and severe thrombocytopenia with or without bleeding from other parts of the body.⁸

Taking this background we planned a study to note the liver dysfunction of patient admitted with *Plasmodium vivax* malaria.

MATERIAL AND METHODS

A prospective study was planned from October 2015 to October 2016 in S.N. Medical College, Agra. A total of 200 patients were included who were older than 14 years of age and of either sex, who were willing to give consent, and had thin and thick peripheral smear positive for *P. vivax*. Further all *P. vivax* cases enrolled in the study underwent OPTIMAL malarial antigen test to rule out mixed malarial infection.

Patients with mixed malarial and dengue infection, pregnant female and those who refused to give the written consent were excluded from this study.

Detailed history and clinical examination was noted. Routine hematological and biochemical investigation were carried out as per treating physician's decision. Chest radiograph and ultrasonography of abdomen were recorded in all patients. Estimation of blood glucose, coagulation profile for disseminated intravascular coagulation (DIC), blood cultures and arterial blood gas analysis were carried out when indicated. Serum was tested for bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, protein, albumin, urea, creatinine. Serological test for HIV, hepatitis B and C and dengue IgM.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the analysis. Descriptive statistics were used for the analysis.

RESULTS

Out of 200 patients, 96 were males and 104 were females i.e. both sexes were almost equally affected. In the study group maximum 122 (61.0%) patients belonged to age group 15-30 years, suggesting that *P. vivax* malaria is more prevalent in younger age group (tables-1,2).

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Out of 200 patients 54 (28%) have serum bilirubin >3mg/dl among them 39 (72.2%) were females out of 54 (27.8%) patients and 15 were males out of 54 patients indicating that females have more liver dysfunction than males.

Age and sex wise distribution of patients having serum bilirubin >3mg/dl, 30 patients out of 54 were between 14-30 years of age which was 55.5% which implies that liver dysfunction is more common in younger patients (table-3).

Out of 200 patients 48 patients have serum bilirubin between 3-10mg/dl and 6 patients have serum bilirubin >10mg/dl.

Out of 54 patients having serum bilirubin >3mg/dl, 33 patients have more increase indirect bilirubin and 21 patients have increase direct bilirubin.

Out of 200 patients liver enzymes SGOT was found between 40-120 in 99 patients (57 females and 42 males) and >120 IU/L was found in 42 patients (24 females and 18 males). SGPT was raised between 40-12- in 99 patients (60 females and 39 males) and >120 in 12 patients (9 males and 3 females) (tables-4-7).

42 females out of 104 developed jaundice and 30 males out of 96 developed jaundice.

DISCUSSION

In the last few years many cases of severe Plasmodium vivax (p. vivax) malaria were seen and some cases resulted in death. The severe manifestations in p.vivax malaria as

reported include cerebral malaria, hepatic dysfunction, acute respiratory distress syndrome, multiple organ dysfunction. Malaria continues to be a huge, social, economical health problem, mainly in tropical countries. The major cause for mortality and morbidity is complicated malaria. Early diagnosis and prompt treatment of complications reduces the global burden. Very few studies are available in the context of p. vivax malaria for the prevalence of liver dysfunction but it has been vastly studied in malaria caused by plasmodium falciparum.

Jaundice has been one of the common complication associated with complicated p.vivax malaria.¹¹ Jaundice can occur in malaria due to various reasons, intravascular hemolysis, disseminated intravascular coagulation has been the well known causes. One of the common reason for jaundice in P. vivax malaria turns out to be malarial hepatitis^{7,12}

Due to lack of research in p. vivax malaria the exact pathogenesis and organ specific morbidity caused by p. vivax infection remains unrecognized and poorly studied. Plasmodium vivax is widely believed to be incapable of causing cyto-adherence and microvascular sequestration

	Clinical feature	No. of patients
1.	Fever	200 (100%)
2.	Jaundice	72 (36%)
3.	Pallor	82 (41%)
4.	Hypotension	20 (10%)
5.	Hemolysis	42 (21%)
6.	D.I.C.	10 (5%)
7.	Hepatomegaly	40 (20%)
8.	Thrombocytopenia	148 (74%)
9.	Altered sensorium	4 (2%)
10.	Nausea and vomiting	75 (37.5%)
11.	Oliguria	37 (18.5%)
12.	Headache	77 (38.5%)
13.	Pain abdomen	29 (14.5%)
14.	Splenomegaly	69 (34.5%)

Table-1: Clinical feature

Age	Male	Female	Total
15-30	54	68	122 (61%)
31-45	23	16	39 (19.5%)
46-60	12	15	27 (13.5%)
>60	7	5	12 (6%)
Total	96	104	200

Table-2: Patient distribution according to age and sex

Serum bilirubin	Male		Female		Total
	No.	%	No.	%	
<3 Mg/dl	81	40.5	65	32.5	146
>3 Mg/dl	15	7.5	39	19.5	
Total	96	48	104	52	200

Table-3: Impact of malaria on serum bilirubin

Age groups	No of patients S. bill >3mg/dl				
	Male		Female		Total
	No.	%	No.	%	No.
14-30 years	12	6	18	9	30
31-45 years	0	0	9	4.5	9
46-60 years	3	1.5	6	3	9
>60 years	0	0	6	3	6
Total	15	7.4	39	19.5	54

Table-4: Age and sex wise distribution of patients having S.bilirubin >3mg/dl

S. Billirubin	Male		Female		Total
	No.	%	No.	%	
3-10mg/dl	15	7.5	33	16.5	48
>10mg/dl	0	0	6	3	6
TOTAL	15	7.5	39	19.5	54

Table-5: Distribution of patients according to S. bilirubin

Liver enzymes		Male		Female		Total
		No.	%	No.	%	
SGOT (IU/L)	40-120	42	21	57	28.5	99
	>120	18	9	24	12	42
SGPT (IU/L)	40-120	39	19.5	60	30	99
	>120	9	4.5	3	1.5	12
Total		108		144		

Table-6: Distribution of patients according to raised liver enzymes

Jaundice	Sex			
	Male		Female	
	No.	%	No.	%
0 (No)	66	33	62	27.69
1 (Yes)	30	15	42	20.77
Total	96	48	104	52

Table-7: Jaundice percentage

and therefore unable to cause organ dysfunction. Recent observation have shown evidence of parasite in lung vasculature during evaluation of lung injury in *P. vivax* malaria.¹³ There are many reports of *p.vivax* malaria producing severe and fatal complication like severe jaundice, acute respiratory distress syndrome, severe anemia, multi organ failure, thrombocytopenia, renal failure etc. comparable to *falciparum* malaria.¹⁴ The mechanism of organ involvement in *P. vivax* infection are still questionable. Sequestration of the parasitized red cells in the capillaries, enhanced inflammatory and immunological response as indicated by increased level of C- reactive protein, TNF-alpha, IFN- gamma as indicated by various studies, caused be the possible reason.¹⁵⁻¹⁸

In the present study, the female to male ratio was 1.08:1. Echeverri et al¹⁹ in Colombia reported M: F ratio was 1.85:1 and Milind Nadkar et al²⁰ male to female ratio was 2.56:1. In our study, maximum 61% cases were seen in the age group of less than 30 yrs. followed by 19.5% in 31-45 year 13.5% in 46-60 years. The mean age of participants in our study was 34.4 years. The study by Milind Nadkar et al²⁰ also reported the same mean age. But in study conducted by Echeverri et al¹⁹ in Columbia the mean age was 23 yers and in study by Kocher et al²² it was 29.65 years.

In our study jaundice was seen in 36% while in other study done by Sarkar et al²³ reported jaundice in 66% of cases which is very high, it might be due to inclusion of only severe malaria patients in their study, whereas in our study we included all mild, moderate and severe cases of *plasmodium vivax* malaria.

Guha et al²¹ suggested that the implication of oxidative stress induced mitochondrial pathway of apoptosis in the pathophysiology of hepatic dysfunction in malaria. Malarial infection induces the generation of hydroxyl radicals (OH) in liver, which may be responsible for the induction of oxidative stress and apoptosis. Apoptosis in hepatocytes has been confirmed by terminal deoxynucleotidyl transferase (TdT) mediated dUTP-biotin nick end labelling assay (TUNEL) and caspas-3 activation. Administration of OH specific antioxidants as well as spin trap alpha-phenyl-tert-butyl-nitron in malaria infected mice significantly inhibits the development of oxidative stress as well as induction of apoptosis.

S. bilirubin (>3 mg /dl) was seen in 27% of *P. vivax* cases in our study, but in study done by M K Mahapatra et al¹⁷ S.bilirubin >3mg/dl in 7.2% of the cases.

Hepatomegaly present in 20% of cases and splenomegaly were noted in 34.5% of cases in our study. Echeverri et al¹⁹ reported 17% and 10% of cases with hepatomegaly and splenomegaly respectively in their study.

When the subsides and parasites clears from the body, liver dysfunction usually resolves and serum bilirubin starts receding normally by 72 hours after starting antimalarial treatment however, it may be delayed in patients having co-existing renal dysfunction.²⁴

CONCLUSION

As evidence from various studies, *p.vivax* malaria is no

longer a 'benign' disease and it can produce jaundice, hepatic dysfunction and anemia. In view of liver dysfunction, the clinician should be very vigilant while treating the case of *p.vivax* malaria and always look for the complications which are otherwise very common in *p.falciparum* malaria. Jaundice is commonly mistaken for hepatitis in rural practice. Hence, the patients who have fever and jaundice, should always be investigated for *P.vivax* malaria.

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