Hepatic and renal dysfunctions in a malaria endemic region: falciparum malaria vs vivax malaria

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Abstract

Malaria is a major health problem in the tropics. Liver dysfunction has been a common finding in malaria patients. Malaria causes inhibition of certain liver functions without showcasing signs of hepatic insufficiency. After termination of such attack, normal liver may be restored but a continued low-grade malarial infection can cause permanent liver damage. This retrospective study was done in order to study the proportion of hepatic and renal involvement to find possible ways of modifying the clinical outcomes. All malaria positive cases from June 2012 to June 2015 in Kasturba Medical College hospitals were included. The patients were stratified into 3 groups based on the type of malaria Group I – *P. vivax*, Group II – *P.falciparum* and Group III- mixed (*P.falciparum* and *P.vivax*) and sub-divided based on age and sex. Their hepatic and renal functions were evaluated. Statistical analysis was done using SPSS vers.11.5 using descriptive analysis and ANOVA. A total of 2139 cases of malaria were diagnosed based on their peripheral blood pictures of which males (75%) outnumbered females (25%). In the three groups the proportion of infection was 81.5%, 3.4%, and 15.1% respectively and hepatic dysfunction was 57.3%, 39.2% and 74.7% respectively. Out of the 67 *P.falciparum* infected patients 70% had renal dysfunction. 61% patients had anaemia. We conclude that malaria is a major health concern in this region, majority being infected with *P.vivax*. The proportion of patients having severe manifestations like severe anaemia, jaundice, hypoalbuminemia and hepatopathy was more significantly associated with mixed malaria followed by *P.vivax.*

Keywords: Malaria, Liver function test, *Plasmodium vivax*, *Plasmodium falciparum.*

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Introduction

Malaria has been troubling India and other tropical and subtropical areas of the world since ancient times.[1,2] A mention about this disease has been made in ancient Indian medical literature such as Atharva Veda and Charaka Samhita.[3] It is a vector borne parasitic disease caused by the genus *Plasmodium.*[4] India's diverse geography and climate provide ideal environment for the survival and also for sustaining malaria parasites and their vectors. The incidence of malaria has increased with urbanization.[5,6] Four species of *Plasmodium* traditionally responsible of human malaria are *Plasmodium falciparum, P.vivax, P.malariae* and *P.ovale*. Rarely, several simian species can infect human beings, either naturally or on accidental exposure, such as *P.knowlesi, P.brasilianum, P.cynomolgibastianelli, P.schwetzi* and *P.inui.*[4] Among all the species of *Plasmodium*, most commonly observed in India are *P.falciparum* and *P.vivax.* A very few *P.malariae* cases have been reported from Karnataka and Orissa.[7]

The consequences of human erythrocytic invasion and destruction by the parasite and the host's response are responsible for all the clinical symptoms.[8,9] Malaria is well known for its morbidity and mortality. *P.vivax* is more benign compared to *P.falciparum*. Complications and fatality are predominantly seen in *P.falciparum* infections. However, an increase in the number of cases of complications has been reported with *P.vivax* infection as well. The commonest complications associated are cerebral malaria, severe haemolytic anaemia, pulmonary oedema, acute respiratory distress syndrome (ARDS), thrombocytopenia, disseminated intravascular coagulation, shock, renal involvement, kidney failure and hepatic dysfunction.[7,10-12]

Hepatic dysfunction has been a common finding in malaria patients. Malaria causes inhibition of certain liver functions without showcasing signs of hepatic insufficiency. After termination of such attack, normal liver may be restored but a continued low-grade malarial infection can cause permanent liver damage. According to WHO, signs of hepatic dysfunction except for jaundice are unusual; also asterexis and other clinical signs of liver failure can never be seen unless there is concomitant viral hepatitis. However, recently a number of cases with definite evidence of hepatic encephalopathy have been reported from India and all over the world.[13,14] The spectrum of hepatocellular dysfunction varies from mild derangement of liver function tests to those describing liver failure as a complication of falciparum malarial infection. Often the term 'malarial hepatitis' is used for hepatocellular jaundice in patients with malaria, the clinical significance of which is not yet elucidated.[15]

This study was done with the objectives to study the proportion of hepatic and renal involvement in

malaria patients to find possible ways of modifying the clinical outcomes.

Materials and Method

A retrospective descriptive study was conducted which included all the patients diagnosed with malaria by peripheral blood smear from June 2012 – June 2015at KMC hospital, Ambedkar Circle; KMC hospital, Attavar and government Wenlock hospital. Data was collected regarding the liver functions of the patients which will include serum bilirubin levels, liver enzymes like alanine transaminase (ALT), aspartate transaminase (AST), serum albumin and haemoglobin.

Inclusion criteria: All patients diagnosed as malaria positive

Exclusion criteria: Patients with confirmed alternate diagnosis of liver or kidney disease.

Statistical analysis: A statistical package SPSS vers.11.5 was used to do the analysis, Chi square test was used to analyze the data. $p < 0.05$ was considered as significant.

Results

A total of 2139 cases of malaria were diagnosed based on their peripheral blood picture. In the three groups of vivax, falciparum and mixed malaria, the proportion of infection was 81.5%, 3.4%, and 15.1% respectively (Fig. 1). Table 1 shows the percentage wise sex distribution in malaria subtypes. The comparison of biochemical parameters between male and female patients are described in Tables 2. Hepatic dysfunction was 57.3%, 39.2% and 74.7% in the groups – vivax, falciparum and mixed malaria respectively. Out of all the *P.falciparum* infected patients, 70% had renal dysfunction and 61% patients had anaemia (Tables 3, 4).

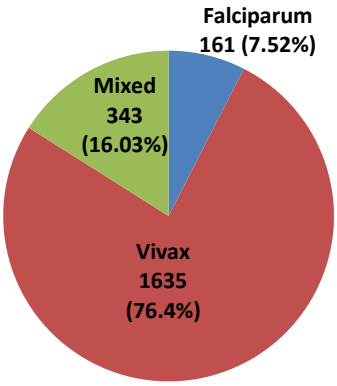

Fig. 1: Malaria Subtypes (n=2139)*

***(**Maroon fraction – Vivax malaria, Blue fraction – Falciparum malaria, Green fraction – Mixed malaria)

Table 1: Percentage wise sex distribution in malaria subtypes

Subtypes	Number of Cases		
Males-Falciparum	129	8% (males)	75%
Males-Vivax	1229	76.5% (males)	
Males-Mixed	248	15.4% (males)	
Females-Falciparum	32	5.9% (females)	25%
Females-Vivax	406	76.03% (females)	
Females-Mixed	95	17.8% (females)	

The percentages of infection of malaria subtypes are similar in males and females with vivax contributing the most and falciparum least.

Table 2: Comparison between Males and Females

Parameter	Male	Female	p value
N	1606	534	
Age	36.34±17.40	39.63±20.50	0.002
T.Bil	2.29±2.89	1.965±2.679	<0.001
D.Bil	1.1±2.57	0.95±1.95	0.001
T.protein	6.38±0.77	6.23±0.802	<0.001
Albumin	3.52±1.94	3.25±0.62	<0.001

AST	47.63±45.03	44.44±43.13	0.011
ALT	43.39±37.06	40.39±38.79	0.002
ALP	102.28±61.56	106.42±54.76	0.038
Urea	39.01±24.96	37.24±22.69	0.013
Creatinine	1.24±1.17	1.28±4.42	<0.001
Hb	12.26±3.53	11.11±7.47	<0.001

All parameters were significantly high in males when compared to females

(The larger the sample size, the more likely a hypothesis test will detect a small difference. Thus it is especially important to consider practical significance when sample size is large)

Table 3: Comparison between malaria subtypes

Parameter	Falciparum	Vivax	Mixed	p value
N	161	1635	343	
Age	37.26±16.12	36.64±18.29	39.58±18.95	0.026
T.Bil	2.59±3.29	2.09±2.70	2.63±3.23	0.001
D.Bil	1.75±5.62	0.96±1.85	1.25±2.33	0.000
T.protein	6.31±0.82	6.36±0.79	6.29±0.69	0.254
Albumin	3.37±0.74	3.46±1.72	3.42±2.02	0.093
AST	64.07±75.04	45.62±42.62	44.53±31.18	<0.001
ALT	53.57±59.91	40.92±34.62	45.64±36.29	<0.001
ALP	104.84±53.16	102.65±60.4	105.99±61.13	0.292
Urea	45.65±39.11	37.83±22.89	38.83±22.15	0.234
Creatinine	1.32±0.82	1.18±1.15	1.54±5.49	<0.001
Hb	11.76±2.79	11.94±3.81	12.24±8.62	0.246

Table 4: Comparison between males and females in each malaria subtypes*

(i) Falciparum

Parameter	Male	Female	p value
N	129	32	
Age	36.5±15.38	41.21±19	0.2
T.Bil	2.59±3.35	2.54±3.04	0.670
D.Bil	1.90±6.15	1.07±2.33	0.452
T.protein	6.31±0.83	6.32±0.82	0.916
Albumin	3.42±0.74	3.18±0.69	0.102
AST	67.26±76.14	49.94±68.91	0.027
ALT	56.25±62.12	41.41±48.55	0.185
ALP	106.87±52.58	96.06±54.71	0.129
Urea	46.07±40.23	45.43±35.13	0.693
Creatinine	1.35±0.82	1.21±0.79	0.054
Hb	12.05±2.79	10.61±2.45	0.008

(ii) Vivax

Parameter	Male	Female	p value
N	1229	406	
Age	36.03±17.62	38.47±20.16	0.041
T.Bil	2.18±2.82	1.81±2.28	<0.001
D.Bil	0.97±1.87	0.91±1.81	0.024
T.protein	6.41±0.77	6.20±0.84	<0.001
Albumin	3.53±1.94	3.24±0.62	<0.001
AST	46.00±42.02	44.42±44.31	0.025
ALT	41.59±33.28	38.91±38.32	0.001
ALP	101.22±61.92	106.88±55.28	0.026
Urea	38.12±22.85	36.86±22.84	0.017
Creatinine	1.22±1.22	1.06±0.89	0.016

Hb	12.33±3.76	10.75±3.68	<0.001

(iii) Mixed

Parameter	Male	Female	p value
N	248	95	
Age	37.91±17.44	43.92±21.91	0.018
T.Bil	2.71±2.96	2.41±3.85	0.010
D.Bil	1.31±2.33	1.09±2.34	0.029
T.protein	6.29±0.72	6.29±0.63	0.938
Albumin	3.48±2.34	3.24±0.57	0.329
AST	45.51±34.21	41.96±21.32	0.837
ALT	45.64±36.24	45.63±36.62	0.952
ALP	105.17±64.06	108.13±52.98	0.259
Urea	39.79±24.20	36.32±15.40	0.275
Creatinine	1.28±1.05	2.22±10.30	0.001
Hb	12.03±2.56	12.79±15.91	<0.001

*(Tb: Total bilirubin, Db: Direct bilirubin, Tp: Total protein, Alb: Albumin, Ast: Aspartate transaminase, Alt: Alanine transaminase, Alp: Alkaline phosphatise, Creat: Creatinine, Hb: Haemoglobin)

Discussion

Malaria is well-known for its morbidity and mortality in India. Among the four species of Plasmodium, *P.falciparum* and *P.vivax* are commonly found in our country. Most of the complications are usually associated with *P.falciparum* malaria. *P.vivax* malaria is considered to be benign malaria with a very low case-fatality ratio but still it may cause a severe and debilitating febrile illness as in *P.falciparum* malaria.[7]

Studies in the Asian continent[1,16] have shown that *P.vivax* malaria accounts for a substantial proportion of hospitalized patients which was also observed in the present study. The proportion of infection was 81.5%, 3.4%, and 15.1% from the groups: vivax, falciparum and mixed malaria respectively (Fig. 1).

Liver involvement: Liver is involved in malaria at two stages:

a. **The pre-erythrocytic cycle:** In this phase it is linked to the binding of the merozoite circumsporozoite protein CSP-A and tartarate resistant acid phosphatase (TRAP) protein to the hepatocytes via the heparan sulphate glycosylaminoglycans (GAG) which promotes minimal liver damage.[15]
b. **The erythrocytic phase:** In this phase, jaundice is a common remark and it is directly caused by the:
   1. **Infection:** malarial hepatitis, intravascular hemolysis of parasitized RBC, septicemic hepatitis.
   2. **Indirect causes:** microangiopathic hemolysis associated with DIC, G6PD-related hemolysis, antimalarial drug induced-hemolysis.
   3. **Completely unrelated:** coexisting acute viral hepatitis, underlying chronic hepatitis.[9,15]

It was found that hepatic dysfunctionwas present in 57.3%, 39.2% and 74.7% of the vivax, falciparum and mixed cases respectively in this study (Tables 3, 4).

Kidney involvement: Kidneys in malaria are involved in two different manners: acute and chronic diseases.

a. Acute renal failure (ARF) is one of the most challenging diseases in tropical countries and malaria plays important epidemiological role.[1,7,9,11,15,17-19] The mortality due to malaria ARF is high.[19]
b. Chronic and progressive glomerulopathy is mainly known in *P.malariae*.[9]

The clinical presentation with renal failure and shock has also emerged as a statistically significant manifestation of falciparum malaria from 2001.This relates to the present study where out of all the *P.falciparum* infected patients, 70% had renal dysfunction and 61% patients had anaemia. These observations have also been reported from Vietnam and different parts of India.[19] A correlation with severity of malaria with thrombocytopenia has also been described.

Depending on the severity and rapidity of infection and immune system of the host, the spectrum of severe malaria differs from area to area and at different times in the same area. The knowledge of the changing spectrum in the region is very essential to the health care providers working in the community. The recent data percolating from different areas of India reflects a drastic change in favour of renal and hepatic involvement. Jaundice may be present in all forms of human malaria but tends to be more severe in *P.falciparum* infection.[17] A similar observation was made in our study.

The pathogenicity of severe malaria infection is complex and it is regulated by both parasite and host factors. Adequate clinical management of malaria patients requires first an accurate diagnosis, then appropriate antimalarial treatment, associated with

adjunct supportive therapies which need to be adapted to the different clinical presentation of the disease.[9]

Awareness of the relative prevalence of different complications in a particular geographic area could greatly facilitate the approach towards early diagnosis and prompt treatment.[17] This is very vital because many other infective diseases presently prevalent in the community have similar clinical presentation.

Limitation of the study

A prospective study could be undertaken to determine not only the complications of the infection but also to know the implication of the complications by following up to see the outcome. Nonetheless a retrospective study will help us to know the proportion of hepatic and renal involvement in malaria infection.

Conclusion

We conclude that

- Malaria is a major health concern in this region, majority being infected with *P.vivax*.
- The proportion of patients having severe manifestations like severe anaemia, jaundice, hypoalbuminemia and hepatopathy was more significantly associated with mixed malaria followed by *P.vivax*.
- Adequate clinical management of malaria patients requires an accurate diagnosis, appropriate antimalarial treatment and adjunct supportive therapies, adapted to the different clinical presentation of the disease.
- The knowledge of the changing spectrum of malaria in the region is very essential to the health care providers working in the community.
- Awareness of relative prevalence of complications in malaria in a particular geographic area could greatly facilitate the approach towards early diagnosis and prompt treatment because many other infective diseases in the community have similar clinical presentation.

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