Original Article

PLASMODIUM FALCIPARUM VERSUS PLASMODIUM VIVAX: WHICH IS A LESSER EVIL?

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ABSTRACT

Background: With changing spectrum, different grades of biochemical & haematological changes generally found to be more severe with p. falciparum, now frequently seen with p. vivax. Present study intends to find species specific differences in diseases progression & complications.

Methodology: A retrospective study of Malaria-patients admitted at GMERS Medical College & Hospital, Vadodara from january-2011to december-2011 was done. p. falciparum, P. Vivax were diagnosed by demonstrating asexual forms of parasites in peripheral blood smear, haematological & biochemical tests were analyzed.

Results: Out of 1093 cases, 781 were slide positive, remaining 312 were treated on clinical-ground .Of 781 cases, 443 (56%) p. falciparum, 327 (42%) P. Vivax and 11(2%) were mixed Infection. Male to female ratio was 1.8:1&0.8:1 in p. falciparum & P. vivax, respectively. Fever, Prodroms, GI symptoms, Liver -dysfunction (51%vs47%), Renal- dysfunction (52%vs48%) were equally frequent; whereas Hemolysis, Bleeding tendency, Breathlessness and altered sensorium were more in p. falciparum. Anemia (56%), Thrombocytopenia (60%), Pancytopenia (54%), Hemolysis (65%) was more frequent in p. falciparum. Leucopenia (54%) was more frequent in p. Vivax.

Conclusion: In contrast to earlier studies, which have proven p. falciparum to be more fatal & complicated, it was noted in present study that P. Vivax species was frequent cause of overall slide-positive cases causing complications head to head with p. falciparum. Anemia, Hepato-renal dysfunctions were equally frequent, nonfatal leucopenia more in p. Vivax, while hemolysis and thrombocytopenia was more in p. falciparum. If ignored complications can alter clinical course & be equally fatal in p. vivax malaria. Hence p. vivax can no more be considered as benign infection and can be equally lethal.

Keywords: P. falciparum malaria, P. vivax malaria, Leucopenia, Thrombocytopenia, Clinico-pathological profile

INTRODUCTION

Malaria is one of the most important parasitic disease of humans, with transmission in over 100 countries affecting close to three billion people and causing one to two million deaths each year[1]. Malaria is ever-present in the tropics and countries in sub-Saharan Africa, which account for nearly 90 percent of all malaria cases. Large burden of disease is because of p. falciparum, followed by P. vivax. P. falciparum predominates in Africa, New Guinea, (Haiti and the Dominican Republic); p. vivax is more common in the Americas and the western pacific. Southeast Asia contributed to only 2. 5 million cases to the global burden of malaria. According to one study in south-east Asian region, out of approx. 1314 million population at risk for p. falciparum malaria, there are 119 million cases (34%) positive for p. falciparum malaria; out of 1347 million population at risk for p. vivax malaria, there are 90-248 million (63%) positive cases and 156-472 million cases (18%) positive for mixed infection [5], India alone contributed 76% of total cases. In India about two million confirmed cases and 1000 deaths are reported annually. The prevalence of these two species is approximately equal in the Indian subcontinent[2-4].

Malaria is transmitted via the bite of a female anopheles species mosquito, which occurs mainly between dusk and dawn. Other comparatively rare mechanisms for transmission include: congenitally-acquired disease, blood transfusion, sharing of contaminated needles, and organ transplantation. The presenting symptoms of malaria are nonspecific and may also include tachycardia, tachypnea, chills, malaise, fatigue, diaphoresis, headache, cough, anorexia, nausea, vomiting, abdominal pain, diarrhea, arthralgias, and myalgias. Physical findings may include mild pallor, petechie, jaundice, hepatomegaly and/or splenomegaly. [6, 7, 8] Patients with complicated or severe malaria may have hyperparasitemia=100, 000 parasites/micro of blood (=5 to 10 percent of parasitized RBCs); anemia, thrombocytopenia, coagulopathy, elevated transaminases, elevated BUN/creatinine, acidosis, and hypoglycemia [8, 10, 11]. Many of the clinical findings are the result of "cytoadherence" causing small infarcts, capillary leakage, and organ dysfunction; these include the following [9, 10, 11]

Complications in malaria are altered consciousness with or without seizures, respiratory distress or acute respiratory distress syndrome (ARDS), circulatory collapse, metabolic acidosis, renal failure, hemoglobinuria ("black-water fever"), hepatic failure, coagulopathy with or without disseminated intravascular coagulation severe anemia or massive intravascular hemolysis and hypoglycemia.

AIMS & OBJECTIVES

Objectives of the study were to analyze introspect biochemical and haematological changes in malaria and to observe and document species (p. falciparum and p. vivax) related differences in same.

MATERIALS & METHODS:

A retrospective observational randomized study was carried out with selected patients above 12yrs age admitted with clinical diagnosis of malaria from january-2011 to december-2011.

Inclusion criteria:

Patients with age group more than 12 years with symptoms compatible with malaria syndromes like-fever, headache, malaise& prodromal symptoms, diarrhea, vomiting, gastritis, jaundice, bleeding tendency, altered sensorium were included.

Exclusion criteria:

Patients having above symptoms with underlying other diseases causing significant morbidity were excluded, as shown in table 7.

A total of 1093 patients, who presented with symptoms highly suggestive of malaria like fever with chills lasting for more than 24hrs, associated with myriad of symptoms like watery diarrhea, headache, body ache, jaundice, cough, breathlessness, bleeding tendency and altered sensorium. Peripheral smears were scrutinized for malarial parasites. Only those cases with asexual forms of plasmodium in the blood by smear examination for plasmodium were included. The peripheral blood films were prepared from prick of finger, stained by conventional Leishman's stain and Geimsa stain seen under oil immersion (100×) taking care to examine particular upper and lower margins and tail end of the film and a minimum of 100 fields were examined before declaring the slides negative for plasmodium. Various Biochemical

tests like liver, kidney functions, S electrolytes and urine analysis were done in detail. Hematological profile and thin peripheral smear studied in detail for studying severity of thrombocytopenia and leucopenia. Chest x-rays, ultrasound abdomen, serum electrolytes, and neuroimaging were done as and when required for differentiating patients for inclusion and exclusion in study. All patients were scrutinized for increasingly severe cases and for grave prognosis with reference to aforementioned parameters and managed appropriately with supportive treatment like renal replacement (dialysis), ventilators support, blood products and higher antibiotics. Patients with high parasitemic load and other severe complications were treated with inject able Artemisunate (2. 4 mg/kg twice on first day & 2. 4 mg/kg once daily there-after) plus Mefloquine (25 mg/kg in divided doses) and primaquine(1. 5 mg/kg for 14 days in pvivax).

RESULTS

Out of 1093 patients having febrile prodromes and other symptoms compatible for malaria, 781 patients were slide positive and 312 patients were treated with anti-malarial on ground of high clinical suspicion. Of the 781 slide positive patients, 443(56.7%) were p. falciparum cases, 327 (41.9%) were p. vivax cases and 11(1.4%) were mixed infection.

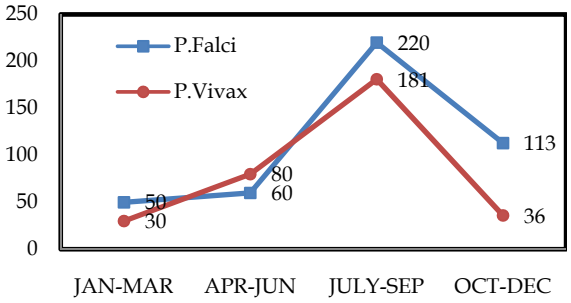

Figure 1: Seasonal distribution of Malaria cases

Table 1: Age and Type-Wise Distribution of Malaria Patients

Age (years)	Type of Malaria (n(%))			Total Patients N(%)	χ^{2*}	P Value
	P. Falciparum	P. Vivax	Mixed infection			
13-20	50(11.29)	47(14.37)	2(18.18)	99(12.68)	1.63	>0.05
21-30	146(32.96)	96(29.36)	4(36.36)	246(31.50)	1.13	>0.05
31-40	109(24.60)	76(23.24)	3(27.27)	188(24.07)	0.19	>0.05
41-50	82(18.51)	63(19.27)	0	145(18.56)	0.07	>0.05
>50	56(12.64)	45(13.76)	2(18.18)	103(13.19)	0.21	>0.05
Total	443(100)	327(100)	11(100)	781(100)		

Table -2: Sex and type wise distribution of Malaria Cases

Age (years)	Type of Malaria (n(%))			Total Patients N(%)	χ^{2*}	P Value
	P. Falciparum	P. Vivax	Mixed infection			
Male	287(67.78)	151(46.18)	7(63.64)	445(56.98)	26.56	<0.01
Female	156(35.22)	176(53.82)	4(36.36)	336(43.02)		
Total	443(100)	327(100)	11(100)	781(100)		

*For table 1 & 2: χ^2Statistic is calculated to observe the significance of difference between P. Falciparum and P. vivax proportions.

Table 3: Clinical Profile and Type Wise Distribution of Malaria Cases

Clinical features	Type of Malaria (n(%))			Total (%)
	P. Falciparum	P. Vivax	Mixed infection	
Fever & prodromal symptoms	430 (97. 06)	314 (96. 02)	11 (100)	745 (95. 39)
Nausea, Vomiting & Diarrhoea	16 (3. 61)	15 (4. 58)	3 (27. 27)	34 (4. 35)
Jaundice	237 (53. 5)	215 (65. 75)	9 (81. 81)	461 (59. 02)
Oliguria	49 (11. 06)	38 (11. 62)	6 (54. 54)	93 (11. 9)
Altered sensorium & convulsion	7 (1. 58)	3 (0. 92)	5 (45. 45)	15 (1. 92)
Bleeding diathesis- Petechie & Hemolysis	78 (17. 61)	35 (10. 7)	9 (81. 81)	122 (15. 62)
Cough and URTI	10 (2. 26)	5 (1. 52)	1 (9. 09)	16 (2. 04)
Anaemia & fatigue	118 (26. 64)	90 (27. 52)	5 (45. 45)	213 (27. 27)
Total	443 (100)	327 (100)	11 (100)	781 (100)

Majority of the patients were in age group of 21-30 years -246(32%), followed by 31-40 years-188 (24%). male to female ratio is 1. 8:1 in p. falciparum malaria and 0. 8:1 in p. vivax malaria (p<0. 01). Severe and complicated cases were 489 in total no., (44%). Severe diseases were (293/443 total p. falciparum cases, approx. 66%) and (196/327 total p. vivax cases, approx. 78%), odds ratio 1. 66. Considering clinical presentation, fever and prodromal symptoms, gastro-intestinal symptoms, jaundice, oliguria, cough and RTI were seen in almost equal number of patients in both subtypes. Bleeding diathesis seen in78 patients of p. falciparum and35 patients of p. vivax malaria, respectively (p<0. 01). Altered sensorium is seen in 7 patients of p. falciparum, 5 patients of p. vivax and 3 patients of mixed infection cases.

Table 4: Severity on Peripheral Smear and Type Wise Distibution of Malaria Cases

Severity	Type of Malaria (n(%))			Total (%)
	P. Falciparum	P. Vivax	Mixed infection	
No thrombocytopenia	75 (16. 93)	88 (26. 91)	-	163 (20. 87)
Grade 1	82 (18. 51)	76 (23. 24)	-	158 (20. 23)
Grade 2	114 (25. 73)	69 (21. 1)	-	183 (23. 43)
Grade 3	172 (22. 57)	94 (28. 75)	11(100)	277 (35. 47)
Total	443 (100)	327 (100)	11 (100)	781 (100)

Table 5: Hematological parameters and type wise distribution of malaria case

Hematology	Type of Malaria (n(%))			Total (%)
	P. Falciparum	P. Vivax	Mixed infection	
Anaemia	118 (26. 64)	90 (27. 52)	5 (45. 45)	213 (27. 27)
leucopenia	162 (36. 57)	198 (60. 55)	3 (27. 27)	363 (46. 48)
Thrombocytopenia	368 (83. 07)	239 (73. 09)	6 (54. 54)	613 (78. 49)
Pancytopenia	6 (1. 35)	3 (0. 92)	2 (18. 18)	11 (1. 42)
Total	443 (100)	327 (100)	11 (100)	781 (100)

Anemia (Hb<7gm%) was seen in 118 cases (56%) of p. falciparum and in total 90 cases(42%) of p. vivax, 5 patients are of mixed infection. Leucopenia was seen in 162 cases (44%) of p. falciparum, 198 cases (54%) of p. vivax malaria (p<0. 01). Thrombocytopenia was noted in 368 cases (60%) of p. falciparum and 239 cases (38%) of p. vivax malaria (p<0. 01). considering severity of thrombocytopenia total 172 cases(62%) p. falciparum and 92(33%) p. vivax patients were having grade3 thrombocytopenia (p<0. 01). Pancytopenia was seen in 6 cases (54%) p. falciparum, and 3 cases (27%) of p. vivax patients. Altered liver function test or malarial hepatopathy (increased S. bilirubin, SGPT) was seen in 237 cases(51%) p. falciparum, 215 cases (65%) p. vivax patients (p<0. 01). raised indirect bilirubin seen in 58cases(13. 09%) of p. falciparum and 23 cases(7. 03%) of p. vivax malaria, (p<0. 01). renal dysfunction was seen in 49cases (11. 06%) of p. falciparum and 38cases (11. 6%) of p. vivax malaria, respectively.

DISCUSSION

Malaria is still a leading health hazard is changing its face periodically. Severity of the disease is seen to 100 lose species specificity in mostly non-immune individuals especially in endemic and hyper-endemic regions.

Table 6: Biochemical parameters and type wise distibution of malaria cases

Biochemical Parameters (LFT/RFT)	Type of Malaria (n(%))			Total (%)	X^2	p-value
	P. Falciparum	P. Vivax	Mixed infection			
Raised total Bilirubin, SGOT, SGPT	237 (53. 5)	215 (65. 75)	9 (81. 81)	461 (59. 03)	11. 65	<0. 01
Raised indirect bilirubin	58 (13. 09)	23 (7. 03)	7 (63. 63)	88 (11. 27)	7. 34	<0. 01
Raised serum creatinine	49 (11. 06)	38 (11. 62)	6 (54. 54)	93 (11. 90)	0. 06	>0. 05
Total	443 (100)	327 (100)	11 (100)	781 (100)		

* X2 statistic is calculated to observe the significance of difference between P. falciparum and P. vivax proportions

Table 5: Associated co-morbid Conditions and Type Wise Distribution of Malaria Cases

Associated Disease	Type of Malaria (n(%))			Total (%)
	P. Falciparum	P. Vivax	Mixed infection	
Tuberculosis	3 (0. 68)	1 (0. 30)	-	4 (0. 51)
Diabetes mellitus	5 (1. 13)	2 (0. 61)	-	7 (0. 90)
IHD	4 (0. 90)	3 (0. 92)	-	7 (0. 90)
Urinary tract infection	7 (1. 58)	9 (2. 75)	-	16 (2. 05)
Enteric fever	3 (0. 63)	4 (1. 22)	-	7 (0. 90)
Upper resp. tract infection	11 (2. 48)	7 (2. 14)	-	18 (2. 30)
Lower resp. tract infection	4 (0. 90)	3 (0. 30)	-	7 (0. 90)
Acute gastroenteritis	7 (1. 58)	7 (2. 14)	-	14 (1. 79)
Hypothyroidism	4 (0. 90)	7 (2. 14)	-	11 (1. 41)
Total	443 (100)	327 (100)	11 (100)	781 (100)

Although most severe and complicated malaria is usually due to p. falciparum, patients with complicated infection due to p. vivax have also been described in recent times. As per study of White & Bremen for study of severity of malaria & malaria affecting pregnant, those at greatest risk for severe disease include non-immune individuals, immune-compromised patients (including asplenic individuals), and children 6 to 36 months of age, and pregnant women. Increasing parasitemia is associated with increasing disease severity. Semi-immune individuals may have substantial parasitemia with few or no clinical manifestations[8, 12]. Our study has shown that the number of severe complicated cases were relatively more in P. vivax to that of P. falciparum (78%against 66%). This may be due to change in the genetic structure of P. vivax species or more number of non-immune individual getting infected with new Strain. Population migration could also contribute to species specific predominance. Multidrug-resistant plasmodium vivax is emerging in Asia-pacific and South America. P Vivax malaria generally regarded as a benign disease, is getting more complicated now a days. In our study, maximum numbers of cases were seen in 21 to 40 years of age group, which is most productive age group. P. falciparum malaria is seen more in males whereas p. vivax malaria is seen more in females. Fever with prodromal symptoms is still leading picture of presentation, whereas one should be highly suspicious of malaria when pt presents with fever associated with deranged or altered renal, hepatic hematological, neurological and gastrointestinal function.

Hematologic abnormalities

Anemia in the setting of malaria occurs as a result of hemolysis of parasitized red cells, increased spleenic sequestration and clearance of erythrocytes with diminished deformability, cytokine suppression of hematopoiesis, shortened erythrocyte survival, repeated infections and ineffective treatments. Poor outcome was seen in patients with parasitemia (>500, 000 parasites/mm3 or >10, 000 mature trophozoites and schizonts/cmm) and 5 percent of neutrophils containing malarial pigment. As studied by Roberts D. J & Abdalis in their studies P. falciparum can invade red cells of all ages, including cells as early as orthochromatic erythroblasts [15]. Parasitemia is often high occasionally exceeding 50%. . The anemia of p. falciparum malaria is typically normocytic and normochromic, with a notable absence of reticulocytes [19, 20]. p. vivax have a strong preference to infect only young red cells (reticulocytes), thereby limiting parasitemia levels to approximately 1 to 2 percent. This was reflected in our study also where presence of anemia was more in pfalciparam(5 6%) against(43%) in P Vivax due to high parasitemic load. Anemia due to hemolysis may be severe, but there is no peripheral sequestration of parasitized red cells.[15,16,17] Maximum cases of anemia due to hemolysis were seen in p falciparum also. Microcytosis and hypochromia may be present due to the very high frequency of thalassemia trait and/or iron deficiency in many patients of the endemic areas [21]. Mild thrombocytopenia and coagulopathy are common in the setting of p. falciparum malaria. Proposed causes for severe thrombocytopenia are, immune complex mediated destruction, spleenomegaly and spleenic sequestration of platelets, cytokine mediated destruction, decreased secretion of thrombopoitin associated with malarial hepatopathy, bleeding with evidence of DIC and ineffective thrombopoeisis.

Out of 213 patients with anemia (HB<7), anemia was almost equally seen in both subgroup of

malaria. Thrombocytopenia was predominantly seen with p. falciparum malaria (368 against 239), relatively more in grade 3 severity group in p. vivax(28% against 22% in P falciparum) malaria requiring platelet transfusion in almost one-third of total severe cases. Our study has noted more number of the patients having nonfatal leucopenia in p. vivax malaria (198 against 164). Antibiotics for control of secondary infection were usually not required. This was probably a reflection of P vivax malaria affecting more premitive WBC cells in Bone marrow The results were similar to study done by Tjitra et al, a prospective study in Papua, Indonesia. Plos med 2008 [15].

Biochemical abnormalities

Biochemical features with grave prognosis are renal impairment (serum creatinine, >3 mg/dl [>265 µmol/liter]), jaundice (serum total bilirubin, >2. 5 mg/dl [>43 µmol/liter]), elevated aminotransferase levels (>3 times normal), the combination of deep jaundice and renal failure is particularly grave. Other parameters are Acidosis (plasma bicarbonate, <15 mmol/liter), hyperlactatemia (venous lactate, >45 mg/dl [>5 mmol/liter]), hypoglycemia (blood glucose, <40 mg/dl [<2. 2 mmol/liter]).

Liver dysfunction

Mild jaundice due to hemolysis in malaria is common as shown in study of White & Breman Severe jaundice due to hemolysis, hepatocyte injury, and cholestasis may occur in the setting of p. falciparum infection; this manifestation is more common among adults than children. Liver dysfunction together with renal impairment and other organ dysfunction portend a poor prognosis[8]. In our study, direct hepatocyte injury with malaria parasite was seen in equal frequency in p. falciparum and p. vivax patients; whereas, increased indirect bilirubin due to hemolysis was seen more in no. in p. falciparum malaria. This shows increasing trend of severe malaria hepatopathy due to various causes due to P vivax malaria although number is still less than p. falciparum.

Renal dysfunction

Acute renal failure (ARF) is seen mostly in plasmodium falciparum infection, but p. vivax and p. malariae can occasionally contribute for renal impairment. Malarial ARF is commonly found in non-immune adults and older children with falciparum malaria. Occurrence of ARF in severe falciparum malaria is quite common in southeast-Asia and Indian subcontinent. Since precise mechanism of malarial ARF is not known, several hypotheses including mechanical obstruction by infected erythrocytes, erythrocyte sequestration interfering with renal microcirculatory flow and metabolism, immune mediated glomerular and tubular pathology, fluid loss due to multiple mechanisms (hypovolemia and hemolysis) and alterations in the renal microcirculation, etc, have been proposed [13]. Large amounts of hemoglobin and malarial pigments may be present in the urine secondary to intravascular hemolysis-an uncommon syndrome known as "black-water fever" manifests in very dark urine following several attacks of falciparum malaria with mortality is high. Mainstay of treatment consists of appropriate anti -malarial drug therapy, fluid replacement, and renal replacement therapy. Renal impairment can manifest as acute tubular necrosis (both clinically and pathologically), although renal cortical necrosis does not occur. In our study, the patients with deranged renal function were seen equally in both species, however, aggressive renal replacement therapy was required more in P. falciparum malaria. It was noted that renal involvement in early stage of Vivax malaria, if treated aggressively with antimalarials, appropriate and adequate fluids was prevented from progression and need for renal replacement therapy is decreased. These results are similar to study done by Das BS, Journal of vector borne diseases 2008. [22]

CONCLUSION

In earlier studies, p. falciparum malaria was found to be more fatal & complicated than P. vivax malaria. It was noted in present study that P. vivax species was found to be frequent cause of overall slide-positive cases causing complications head to head with p. falciparum this is in contrast with earlier studies. Anemia, Hepato-renal dysfunctions were equally frequent in both types, nonfatal leucopenia more in p. vivax, while hemolysis and thrombocytopenia was more in p. falciparum. If ignored complications can alter clinical course & be equally fatal in P. vivax malaria. Hence P. vivax can no more be considered as benign and can be equally lethal.

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