Original Article

Incidence of Jaundice in Plasmodium Vivax Malaria: A Prospective Study in Moodabidri, South India

Bolar Sadananda Naik

Department of Internal Medicine, Alva's Health Centre, Moodabidri – 574227, Karnataka, India

Submitted: 3 Jan 2014
Accepted: 5 May 2014

Abstract

Background: **A prospective study was taken to look for the incidence of jaundice in *Plasmodium vivax* malaria patients in Moodabidri, a coastal town of South India.**

Methods: **A prospective study was conducted in the patients admitted with the diagnosis of Plasmodium vivax malaria at the Alva's health centre, during study period 1st Jun 2011 to 10th October 2012. Bilirubin levels were checked in all the selected patients. Patients who had their total bilirubin level 3.0 mg% or more were considered to be having jaundice and were further tested for anemia and hepatic dysfunction by carrying out hemoglobin (Hb), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), surface antigen of the hepatitis B virus (HBsAg). The data collected were analysed statistically.**

Results: **A total of 188 patients who had Plasmodium vivax malaria as diagnosed by peripheral blood film (PBF) and rapid diagnostic test (RDT) were included in the study. Jaundice was present in 19 (10.1%) patients and the mean (SD) level of serum bilirubin was 4.5 mg/dL (2.4) (maximum = 12.7 mg %) with 94.7% (n = 18) of the patients having predominantly indirect type or unconjugated hyperbilirubinemia. The hepatic dysfunction was present in 15 (78.9%) with mean (SD) level of aspartate aminotransferase (AST) was 61.57 IU/L (SD 33.8) (maximum = 160 IU/L) and alanine aminotransferase (ALT) was 54.8 IU/L (SD 21.2) (maximum = 108 IU/L). Anemia was present in 3 (15.8%) patients and the mean hemoglobin level was 12.8 gm/dL (SD 1.8) (minimum = 6.4 gm/dL). Out of 19 patients who had jaundice majority were males (94.7 %, n = 18) and only one female (5.3%, n = 1) was found to be having jaundice. The age of the patients who had jaundice ranged from 17 to 60 years 29 years (SD 13.7).**

Conclusion: **This study has further reiterated the fact that *Plasmodium vivax* malaria is no longer a "benign" disease and it can also produce jaundice, hepatic dysfunction, and anemia.**

Keywords: *Plasmodium vivax malaria, jaundice, anemia, hepatitis*

Introduction

Plasmodium vivax malaria is a geographically most widely distributed type of malaria with up to 2.5 billion people at risk and an estimated 80 million to 300 million clinical cases of malaria every year including severe disease and death (1). There has been an increased incidence of *Plasmodium vivax* producing complications in the last five years and there is a need for more detailed epidemiological studies to confirm this (2). *Plasmodium vivax* which was supposed to be causing benign tertian malaria for decades seems to be no longer a non virulent malaria parasite. There are many reports of *Plasmodium vivax* malaria producing complications similar to *Plasmodium falciparum* infection (3,4). With the advent of molecular diagnosis, the *Plasmodium vivax* infection producing complications have become more evident. There are reports of jaundice as the most common complication in Plasmodium vivax infection (2,3,5,6,). Hence, a prospective study was undertaken to look for the incidence of jaundice in *Plasmodium vivax* malaria patients in Moodabidri, South India. Moodabidri is a town in the green valleys of the Western Ghats at Karnataka, South India. This is a small town which has a geographical area of 39.62 square kilometers with a population of nearly 25 000 till last few years. For the last five to six years the population of this town has nearly doubled. There has been a sudden upsurge in the population is due to the enumerable educational institutions set up by the Alva's education foundation over here. In order to accommodate thousands of students, teachers and the support staff of the various colleges, the construction of hundreds of residential apartments were started.

The rain water which got collected on the terraces of these apartments played safe havens for the uncontrolled breeding of the mosquitoes and the spread of malaria subsequently. So, we the clinicians at Moodabidri, who otherwise had very little experience in treating malaria, got a golden opportunity to study the various clinical problems related to the malaria, especially the *Plasmodium vivax*.

Materials and Methods

A prospective study was conducted in the 188 patients admitted with the diagnosis of *Plasmodium vivax* malaria at the Alva's health centre, a multi-specialty hospital located in the town Moodabidri, South India. The study period was from 1st Jun 2011 to 10th October 2012. The patients who had mixed malaria (*P. vivax* malaria co-infected with *P. falciparum*), chronic alcohol abuse, and chronic liver diseases, past history of jaundice were excluded from the study. Bilirubin levels were checked in all the selected patients. Patients who had their total bilirubin level 3.0 mg% or more were considered to be having jaundice and were further tested for anemia and hepatic dysfunction by carrying out Hb, SGOT, SGPT, HBsAg. The other data obtained included age, sex, date of admission and date of discharge of the patients. The data collected were analysed statistically. Data analysis was done by descriptive statistics and the relationship between the variables were estimated by using Karl-pearsons coefficient of correlation. A statistical package SPSS version 17.0 was used to do the analysis. $P < 0.05$ was considered as significant.

Results

A total of 188 patients who had *P. vivax* malaria as diagnosed by PBF and RDT were included in the study.

Jaundice (Table 1) was present in 19 (10.1%) patients and the mean (SD) level of serum bilirubin was 4.47 mg/dL (SD 2.40) (maximum = 12.7 mg %) with 94.7% (n = 18) of the patients having predominantly indirect type or unconjugated hyperbilirubinemia. The hepatic dysfunction was present in 15 (78.9%) with mean (SD) level of AST was 61.6 IU/L (SD 33.8) (maximum = 160 IU/L) and ALT level was 54.8 IU/L (SD 21.2) (maximum = 108 IU/L).

Anemia (Table 1) was present in 3 (15.8%) patients and the mean hemoglobin level was 12.8 gm/dL (SD 1.8) (minimum = 6.4 gm/dL). Out of 19 patients who had jaundice majority were males (94.7 %, n = 18) and only one female (5.3%, n = 1) was found to be having jaundice. The age (Table 1) of the patients who had jaundice ranged from 17 to 60 years. The mean age was 29 years (SD 13.7). In general, out of the 18 male patients who had jaundice 12 (66.7%) patients belonged to the age group of 21 years to 40 years , three (16.7%) patients belonged to the age category of above 40 years and two (11.1%) belonged to the age group of 10 years to 20 years. The sole female patient who had jaundice belonged to the age category of 10 years to 20 years.

Admission and discharge dates were noted in the study to correlate the duration of hospital stay and the severity of jaundice. But, we found the correlation, statistically not significant (Spearman's correlation coefficient r = 0.191, $P = 0.435$).

Discussion

P. vivax malaria which was otherwise considered benign malaria in all these years, has been increasingly presenting with complications akin to *falciparum* malaria. Jaundice has been one of the common problems associated with complicated *P. vivax* malaria (3). Jaundice can occur in malaria due to various reasons. Intra-vascular hemolysis, disseminated coagulation have been the well known causes. Malarial hepatitis is turning out to be one of the common reasons for the jaundice in *P. vivax* malaria (7,8).

We found 19 patients out of 188 *P. vivax* malaria patients having jaundice with an

Table 1: Descriptive statistics of age and blood tests among the patients with jaundice (n = 19)

Variables	Minimum	Maximum	Mean (SD)
Serum Bilirubin (mg %)	3	12.7	4.47 (2.4)
Aspartate Aminotransferase (AST) (IU/L)	14	160.0	61.57 (33.8)
Alanine Aminotransferase (ALT) (IU/L)	16	108.0	54.78 (21.2)
Hemoglobin (gm/dL)	15	6.4	12.80 (1.8)
Age (years)	17	60.0	29.00 (13.7)

incidence of 10.1%. Kochar DK et al. (3) in their study on severe *P. vivax* malaria found jaundice and hepatic dysfunction as the most common complication with an incidence of 57.5% and Charulata S L et al. (9) found an incidence of 5.3% jaundice in their *P. vivax* patients. Similarly, Mohapatra MK et al. (10) found 7.2% incidence of jaundice in their study on atypical presentations of *P. vivax* malaria. The jaundice in our malaria patients was predominantly indirect type or unconjugated hyperbilirubinemia (94.7%, n = 18). But, hepatic dysfunction was present in 15 (78.9%) patients with a mean level of Aspartate Aminotransferase (AST) was 61.6 IU/L (SD 33.8) (maximum = 160 IU/L) and] Alanine Aminotransferase (ALT) level was 54.8 IU/L (SD 21.2) (maximum = 108 IU/L). Many studies have shown a significant rise in the liver enzymes in the patients with *P. vivax* malaria infection (11,12). In view of the presence of hepatic dysfunction and jaundice being predominantly unconjugated type, we are of the opinion that the jaundice in our patients could be due to the combination of both hemolysis and hepatic dysfunction. We could not discuss the incidence of jaundice based on the sex as there was only one woman who got jaundice as compared to the 18 men who got it.

Anemia was present in 15.8% (n = 3) of the patients and the mean hemoglobin level was 12.8 gm/dL (SD 1.8) (minimum = 6.4 gm/dL). In a study on complications of *P. vivax* malaria, Charulata SL et al. (9) found anemia in 3% of their patients and Tjitra et al. (14) found 19% in their study. Anemia in malaria is predominantly due to hemolysis and it is more common in falciparum malaria than *P. vivax* malaria (9). Unlike Plasmodium falciparum infected red blood cells (RBCs), the *P. vivax* infected RBCs show greater deformability while passing the endothelial slits of the splenic sinus and other reticulo-endothelial organs. Thus, the mature RBCs infected with *P. vivax* avoid splenic clearance (15). But, it is the uninfected RBCs which show increased fragility and are removed from the circulation by the spleen, seems to be the important cause of anemia in *P. vivax* malaria (16,17).

Previously, whenever unusual or life threatening complications seen in *P. vivax* malaria, the blame used to be on the possible co-occurrence of undetected *P. falciparum* malaria. Because of this popular belief, the *P. vivax* malaria had been overshadowed by the *P. falciparum*. But, now we know that *P. vivax* could be as dangerous as the falciparum malaria. 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 (3,4,9,14). The mechanisms of organ involvement in *P. vivax* infection are still questionable. Sequestration of the parasitised red blood cells in the capillaries, enhanced inflammatory and immunological response as indicated by increased levels of C- reactive protein, TNF-alpha, IFN- gamma as indicated by various studies, could be the possible reasons (9,18–20).

Conclusion

This study has further reiterated the fact that *P. vivax* malaria is no longer a "benign" disease and it can also produce jaundice, hepatic dysfunction, and anemia. In view of these new developments, the clinicians should be very vigilant while treating the cases of *P. vivax* malaria and always look for the complications which are otherwise very common in *falciparum* malaria. Jaundice is commonly mistaken for hepatitis in rural practice. Hence, in the areas which are endemic for malaria, the patients who have fever and jaundice, should always be investigated for *P. vivax* malaria.

Acknowledgements

The author would like to thank Dr M Chakrapani, Professor of Medicine, Kasturba Medical College, Mangalore for his valuable guidance in preparing the manuscript and Dr Shashidar Kotian, Senior Faculty Member, Department of Statistics, Kasturba Medical College, Mangalore for his help in the statistical analysis of the study. The author would also like to thank Dr Krishna Mohan Prabhu, Prabhu General Hospital, Moodabidri, for helping with the review of literature and Prof SR Tholpady for his help in editing the manuscript for English.

Conflict of Interest

None.

Funds

None.

Correspondence

Dr B SadanandA Naik
MD Internal Medicine (BLR)
Senior Physician
Alva's Health Centre
Moodabidri-574227
Karnataka, India
Tel: +9182-5823 8105
Fax: +9182-5823 6731
Email: sadanandanaik2@gmail.com

Reference

1. Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, Alonso PL, et al. Key gaps in the knowledge of Plasmodium vivax, a neglected human malaria parasite. *Lancet Infect Dis*. 2009;**9**:555–566. doi: 10.1016/S1473-3099(09)70177-X.

2. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. *Lancet*. 2014:**383(9918)**;723–735. doi: 10.1016/S0140-6736 (13)60024-0.

3. Kochar DK, Das A, Kochar SK, Saxena V, Sirohi P, Garg S, et al. Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India. *Am J Trop Med Hyg*. 2009;**80(2)**:194–198.

4. Picot S, Bienvenu AL. Plasmodium vivax infection: not so benign. *Med Sci (Paris)*. 2009;**25(6–7)**:622–626. doi: 10.1051/medsci/2009256-7622.

5. Rizvi I, Tripathi DK, Chughtai AM, Beg M, Zaman S, Zaidi N. Complications associated with Plasmodium vivax malaria: A retrospective study from a tertiary care hospital based in western Uttar Pradesh, India. *Ann Afr Med*. 2013;**12(3)**:155–159. doi: 10. 4103/1596-3519.117624.

6. Yadav D, Chandra J, Aneja S, Kumar V, Kumar P, Dutta AK. Changing profile of severe malaria in north Indian children. *Indian J Pediatr*. 2012:**79(4)**:483–487. doi: 10.1007/s12098-011-0603-x.

7. Anand AC, Puri P. Jaundice in malaria. *J Gastroenterol Hepatol*. 2005;**20**:1322-32. doi: 10.1111/j.1440-1746. 2005.03884.x.

8. Nautiyal A, Singh S, Parmeswaran G, DiSalle M. Hepatic dysfunction in a patient with Plasmodium vivax infection. *MedGenMed*. 2005;**7(1)**:8.

9. Charulata S Limaye, Vikram A Londhey, ST Nabar. The study of complications of Vivax malaria in comparison with Falciparum malaria in Mumbai. *J Assoc Physicians India*. 2012;**60**:15–18.

10. Mohapatra MK, Padhiary KN, Mishra DP, Sethy G. Atypical manifestations of Plasmodium vivax malaria. *Indian J Malariol*. 2002;**39(1-2)**:18–25.

11. Sharma A, Khanduri U. How benign is benign tertian malaria? *J Vector Borne Dis*. 2009;**46(2)**:141–144.

12. Tangpukdee N, Thanachartwet V, Krudsood S, Luplertlop N, Pornpininworakij K, Chalermrut K, et al. Minor liver profile dysfunctions in Plasmodium vivax, P. malaria and P. ovale patients and normalization after treatment. *Korean J Parasitol*. 2006;**44(4)**:295–302. doi: 10.3347/kjp.2006.44.4.295.

13. Gogia A, Kakar A, Byotra SP. Is benign tertian malaria actually benign? *Trop Doct*. 2012;**42(2)**:92–93. doi: 10.1258/td.2011.110295.

14. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, et al. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS Med*. 2008;**5(6)**:e128. doi: 10.1371/journal. pmed.0050128.

15. Handayani S, Chiu DT, Tjitra E, Kuo JS, Lampah D, Kenangalem E, et al. High deformability of Plasmodium vivax -infected red blood cells under microfluidic conditions. *J Infect Dis*. 2009; **199(3)**:445–450. doi: 10.1086/596048.

16. Douglas NM, Anstey NM, Buffet PA, Poespoprodjo JR, Yeo TW, White NJ, et al. The anaemia of Plasmodium vivax malaria. *Malar J*. 2012;**11**:135. doi: 10.1186/1475-2875-11-135.

17. Anstey NM, Douglas NM, Poespoprodjo JR, Price RN. Plasmodium vivax: clinical spectrum, risk factors and pathogenesis. *Adv Parasitol*. 2012;**80**:151–201. doi: 10.1016/B978-0-12-397900-1.00003-7.

18. Anstey NM, Russell B, Yeo TW, Price RN: The pathophysiology of vivax malaria. *Trends Parasitol*. 2009;**25(5)**:220–227.

19. Andrade BB, Reis-Filho A, Souza-Neto SM, Clarêncio J, Camargo LM, Barral A, et al. Severe Plasmodium vivax malaria exhibits marked inflammatory imbalance. *Malar J*. 2010;**9**:13. doi: 10.1186/1475-2 875-9-13.

20. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. *Am J Trop Med Hyg*. 2007;**77(6 Suppl)**:79–87.