Original Article

Clinical Profile of Severe *Plasmodium vivax* Malaria in a Tertiary Care Centre in Mumbai from June 2010-January 2011

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Abstract

Background: *Plasmodium vivax* is the most widely distributed human malaria parasite with an at risk population of 2.5 billion persons. With the implementation of molecular diagnosis, it has become evident that *P. vivax* monoinfection could also result in multiple organ dysfunction and severe life-threatening disease as seen in *P. falciparum* infection.[1,2]

Aims and objectives: To note the clinical profile of patients with severe vivax malaria with regards to demographic, clinical and biochemical profile and its outcome. To compare the profile of falciparum malaria with vivax malaria.

Method and Material: We recruited 711 patients fulfilling the criteria for severe malaria during the study period from June 2010 to Jan 2011. Detailed history and examination findings were noted in all the patients. All the patients were subjected to routine haematological and biochemical investigations. The end points were discharge from wards or death due to malaria.

Results: We had 711 patients with severe malaria of which 488 (68.53%) patients had severe vivax and 223 (31.32%) had severe falciparum malaria. Amongst vivax group, 351 (71.92%) were males and 137 (28.07%) females. Thrombocytopenia (89.13%) was the most common complication followed by renal (31.96%), hepatic (19.46%) cerebral (8.19%) and pulmonary (1.63%) involvement. Most patients were in the age group of 21-30 years and mortality increased with increasing age. The mortality observed in severe vivax malaria was 9.01% (44/488), as compared to falciparum malaria where it was 16.14% (80/223).

Conclusions: Severe vivax malaria is now very common with increasing mortality. The mortality in vivax malaria increases with increasing age. Thrombocytopenia is very common in severe vivax infection. Also, renal, hepatic, lung and cerebral involvement are also occur with increasing frequency. Along with age, severe metabolic acidosis is an independent risk factor for fatal outcome.

Introduction

History is replete with instances of devastation caused by malaria. In India 60 to 65% of the infections are due to *P.vivax* and 35% due to *P. falciparum*. Long considered a benign infection, *Plasmodium vivax* is now recognized as a cause of severe and fatal malaria despite its low parasite biomass, the increased deformability of vivax-infected red blood cells and an apparent paucity of parasite sequestration. The pathogenesis of severe vivax malaria is quite intriguing. Large studies from both halves of the island of New Guinea (Indonesian Papua[3-5] and Papua New Guinea, or PNG[5]) now show a strong association between *P. vivax* infection and severe disease and death. Taking this background, we planned a study in a tertiary care centre in Mumbai from June 2010 to January 2011 to note the clinical profile of patients admitted with severe vivax malaria and to compare it with severe falciparum malaria.

Methods and Material

A prospective study was planned from June 2010 to January 2011 in a tertiary care centre in Mumbai. Patients willing to give consent, older than 12 years of age and of either sex, with smear positive for *Plasmodium* spp. were included in the study. Patients with co-existent vivax and falciparum infection were excluded from the study. All admitted peripheral smear proven *P. vivax* and *P. falciparum* cases of severe malaria fulfilling the inclusion/exclusion criteria were enrolled in the study. Detailed history and clinical examination was noted. All *P. vivax* cases enrolled in the study underwent OPTIMAL malarial antigen test to rule out mixed malaria. A total of 711 patients with severe malaria which excluded mixed infection with *P. vivax* and *P. falciparum* were enrolled in the study during the study period. Of these, 488 were admitted with severe vivax malaria and 223 with severe falciparum malaria. Routine haematological and biochemical investigations were carried out as per treating physician's decision. All patients received injectable artesunate as per hospital policy. Patients were followed up till discharge or death. The study was approved by hospital ethics committee.

Statistical Analysis

Paired t test was applied for comparison of variables like age, duration of symptoms, hemoglobin, platelet count, creatinine, SGOT, SGPT, serum bilirubin. The p value less than 0.05 is considered statistically significant. Chi square test was used for comparing proportions.

Results

Out of 785 admissions of severe malaria defined according to WHO criteria, 711 patients of severe malaria were recruited in the study after excluding cases with mixed vivax and falciparum infection. There were 488 patients admitted with severe vivax malaria, 351 males and 137 females; 223 were admitted with severe falciparum malaria among which 168 were males and 55 were females (Table 1). Table 2 shows age distribution of in severe vivax and falciparum malaria.

44 patients died of severe vivax malaria (9.01%), whereas 36 (16.14%) died of severe falciparum malaria ($p<0.02$). The mortality was almost equal in young adults and elderly in falciparum malaria. However, in vivax malaria group mortality

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Table 1 : Mortality in severe malaria

	Total Malaria*	Vivax Malaria	Falciparum Malaria
Admissions	711	488	223
Deaths	80	44	36
% Deaths	11.25	9.01	16.14**

*Excluding mixed vivax and falciparum infection; **p<0.01

Table 2 : Age of patients with severe malaria and outcome

Age group	Vivax Malaria N=488	Vivax Malaria Deaths N=44	Falciparum Malaria N=223	Falciparum Malaria Deaths=36
12-20years	57 (11.68%)	3 (5.26%)	31 (13.9%)	5 (16.13%)
21-30 years	113 (23.15%)	7 (6.19%)	49 (21.97%)	7 (14.29%)
31-40 years	86 (17.62%)	4 (4.65%)	35 (15.69%)	5 (14.29%)
41-50 years	100 (20.49%)	9 (9.00%)	35 (15.69%)	8 (22.86%)
51-60 years	52 (10.65%)	7 (13.46%)	26 (11.65%)	2 (7.69%)
>60 years	80 (6.14%)	14 (17.5%)*	47 (8.96%)	9 (19.14%)

*P<0.02 for *P.vivax* deaths 12-60 yrs vs. >60 yrs age

Table 3 : Laboratory parameters: vivax malaria vs. falciparum malaria

	Falciparum N=223	Vivax N=488	P value
Hemoglobin (gm %)	9.53±1.98	10.45±1.63	<0.01
Parasitic index%	3.9±4.7	1.06±0.015	<0.0001
Platelet count (/cmm)	41,432±33,036	37,326±24,195	NS
SGOT (IU/L)	73.3±129.6	43.3±145.8	<0.01
SGPT (IU/L)	53.2±75.8	37.2±142	NS
Bilirubin (mg%)	3.68±5.47	1.78±2.79	<0.001
Creatinine (mg%)	2.56±2.18	1.59±1.41	<0.01
Blood pH	7.3±0.12	7.35±0.08	NS

increased with increasing age (Table 2). The mean age of patients who died of falciparum infection was lower compared to vivax infection (44.18±20.96 vs. 51.45±18.57 respectively, p<0.02). The mean age of patients with vivax malaria who died was higher than those survived (51.45±18.57vs. 41.38±18.13 respectively, p<0.001)

The duration of fever before admission was longer in vivax malaria patients who died compared to those who survived (5.20±2.66 vs. 4.33±1.2 respectively, p<0.001). Out of 44 patients who died in vivax malaria group 12 had hypertension, 11 were diabetic and 2 chronic alcoholics. All the 3 pregnant women with severe vivax malaria survived.

Comparison of laboratory parameters between vivax and falciparum malaria is given in Table 3 and Table 4 shows laboratory parameters in vivax malaria patients who died compared to those who survived. The number of organ systems involved in both the groups is shown in Tables 5 and 6.

Discussion

The reported severe manifestations in vivax malaria include cerebral malaria[8], hepatic dysfunction,[9,10] renal dysfunction,[11,12] severe anemia,[9,10] ARDS, and multiple organ involvement. In this prospective study, we recruited 711 patients fulfilling the criteria for severe malaria during the study period from June 2010 to January 2011. Out of these, 488 (68.53%) were admitted with severe *Plasmodium vivax* malaria and 223 (31.32%) had severe *Plasmodium falciparum* malaria (Table 1). Death rate observed in severe falciparum malaria

Table 4 : Laboratory parameters and mortality in vivax malaria

	Survived N=444	Dead N=44	P value
Hemoglobin (gm %)	11.47±1.61	10.7±1.78	NS
Parasitic index%	1.06±0.012	1.05±0.031	NS
Platelet count (/cmm)	60,728±51,354	34,557±17,063	<0.001
SGOT (IU/L)	44.5±152.3	37.1±40.9	NS
SGPT (IU/L)	39.3±148.7	30.45±14.66	NS
Bilirubin (mg%)	1.82±2.84	2.23±2.23	<0.01
Creatinine (mg%)	1.51±1.34	3.39±1.78	<0.01
Blood pH	7.38±0.04	7.31±0.11	<0.01

Table 5 : Number of organs involved in severe vivax malaria

No. of organs involved	Total N=488	Deaths N=44
One organ	279 (57.17%)	17 (6.9%)*
Two organs	165 (33.81%)	23 (13.94%)
Three organs	43 (8.81%)	03 (6.98%)
Four organs	1 (0.20%)	01(100%)

*P<0.01 for vivax malaria mortality with single organ vs. more than one organ involvement

Table 6 : Comparison of organ involvement (severe vivax vs. severe falciparum malaria)

Organ system	Vivax Malaria N= 488	Falciparum Malaria N=223
Thrombocytopenia	435 (89.13%)	178 (79.82%)
Hepatic	95 (19.46%)	81 (36.32%)
Renal	156 (31.96%)	123 (55.15%)
Cerebral	40 (8.19%)	32 (14.35%)
Lungs	8 (1.63%)	5 (2.24%)

(16.14%) was statistically significant as compared to that in severe vivax malaria (9.01%). Sequestration is a specific property of *P falciparum*, this explains for the higher mortality observed in falciparum malaria as compared to vivax malaria. Mortality has been relatively similar across various hospital-based trials regarding severe malaria, despite differences in inclusion criteria, patterns of presenting conditions, and standard of care.

Table 2 compares severe falciparum and vivax malaria with respect to variables. The statistical analysis revealed that patients with severe vivax malaria were significantly older as compared to patients with severe falciparum malaria. The report from Bikaner on case series of severe vivax malaria had mean age of 29.65 ± 11.72 years.[10] Thus our study saw patients admitted with severe vivax malaria in the older age groups. Thus increasing age could indicate a red flag while treating patients with vivax malaria and extra caution could be exerted. The age profile of patients depicts that most of the admitted patients were in the age group of 21- 30 years (Table 2). The factors responsible for the age pattern include outdoor work for young adult males and outdoor sleeping habits which then are more prone to get mosquito bites.

Mortality in vivax malaria increased with age. The reported case-fatality rate associated with severe malaria varies widely. A large multicenter treatment trial conducted in Asia concluded that presenting syndromes in severe malaria depend on age and age is an independent risk factor for a fatal outcome of the disease.[13] This explains the higher proportion of mortality observed in older age groups in our study (Table 2).

Thrombocytopenia was the most common finding in both

falciparum and vivax malaria. Thrombocytopenia was more common in severe vivax malaria as compared to falciparum malaria (Table 6). Bleeding due to thrombocytopenia was seen in the form of epistaxis, melena, petechiae, ecchymoses, hematuria, subdural hematoma all necessitating platelet transfusions.

The frequency of renal failure was 32% in severe vivax malaria and 55% in severe falciparum malaria. The frequency rose to 56.8% and 69.44% in vivax and falciparum malarial deaths. Majority of the patients were treated conservatively with fluid and diuretic therapy, but 29% (45/156) required renal replacement therapy in the form of hemodialysis or CRRT. The maximum creatinine observed in severe vivax malaria was 9.17 mg% whereas that in falciparum malaria was 13.88 mg%. A report on case series of severe vivax malaria done in Bikaner states that complications observed were hepatic dysfunction and jaundice in 23 (57.5%) patients, renal failure in 18 (45%) patients.[10] Thus hepatic dysfunction was the most common complication seen in severe vivax malaria in the study in Bikaner followed by renal failure. The article on burden of malaria in India highlights the increasing frequency of renal failure in severe malaria.[10]

Another study done in Banaras Hindu University concluded that P. vivax malaria can cause ARF, which occurs more commonly in P. falciparum malaria. The prognosis of ARF in P. vivax malaria is favourable.[8] These findings match with those in our study where renal failure was more commonly seen in Falciparum malaria as compared to vivax.

The incidence of hepatic involvement was 19.46% in vivax malaria; whereas it was 36.32% in falciparum malaria. The incidence was 15.9% in vivax malarial deaths. The maximum bilirubin seen was 7 mg% in vivax malaria, whereas that in Falciparum malaria was 38 mg%. None of the patients in vivax malaria group with hepatic involvement had signs of encephalopathy. Hepatic involvement was more common in falciparum malaria and also greater in severity; many had signs of hepatic encephalopathy.

Surprisingly, cerebral involvement was seen in 8.19% of patients with severe vivax malaria. Out of 40 patients with cerebral vivax malaria, 2 succumbed to death. Cerebral malaria was seen in all age groups but maximum patients were in the extremes of their ages i.e. in 2nd and 7th decade. Two patients presented with status epilepticus. Status epilepticus due to *Plasmodium vivax* malaria has been reported in India and Turkey.[14] The possible mechanism for cerebral malaria in vivax malaria has been proposed to be due to nitric oxide production.

We found 8 patients with vivax malaria with ALI/ARDS, out of which 5 succumbed to death. Out of these 5, 3 patients had ALI/ARDS without cerebral, renal or hepatic involvement; 2 patients had multiorgan dysfunction. The proportion mortality was higher in vivax malaria with lung involvement.

The arterial pH in dead patients was significantly lower in dead patients as compared to those who survived of falciparum malaria. The mean pH observed was 7.30 with the lowest value of 7.10. Lactic acidosis has been identified as an important cause of death in severe malaria.[15] Thus our study also came to the same inference that metabolic acidosis is an independent risk factor for outcome of severe malaria.

Almost 82 % of patients who died of severe falciparum malaria had multiorgan dysfunction, whereas 58% of patients who died of severe vivax malaria had multiorgan dysfunction (Tables 5 and 6). The commonest organ combination observed was thrombocytopenia with renal involvement. This was recently reviewed in a WHO sponsored workshop at Rourkela which revealed an increasing trend in favour of renal and hepatic failure and multiple organ dysfunction.

Conclusions

Severe vivax malaria is now very common with increasing mortality. The mortality in vivax malaria increases with increasing age. Thrombocytopenia is very common in severe vivax infection. Also, renal, hepatic, lung and cerebral involvement are also occur with increasing frequency. Along with age, severe metabolic acidosis is an independent risk factor for fatal outcome.

References

1. Barbara S, Focus on Plasmodium vivax. *Trends Parasitology* 2002;18:287–289.
2. Piscot S, Is Plasmodium vivax still a paradigm for uncomplicated malaria? *Med Mal Infect* 2006;36:406–413.
3. Barcus, M.J. et al. Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in north-eastern Indonesian Papua. *Am J Trop Med Hyg* 2007;77:984–991.
4. Tjitra, E. et al. Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. *PLoS Med* 2008;5:e128.
5. Genton, B. et al. Plasmodium vivax and mixed infections are associated with severe malaria in children: a prospective cohort study from Papua New Guinea. *PLoS Med.* 2008;5:e127.
6. World Health Organization Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990;84:S1-S65.
7. World Health Organization Severe falciparum malaria. *Trans R Soc Trop Med Hyg* 2000;94:S1-S90.
8. Beg MA, Khan R, Baig SM, Gulzar Z, Hussain R, Smego RA, Cerebral involvement in benign tertian malaria. *Am J Trop Med Hyg* 2002;67:230–232.
9. Mohapatra MK, Padhiary KN, Mishra DP, Sethy G, Atypical manifestations of Plasmodium vivax malaria. Indian J Malariol 2002;39:18–25.
10. Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, Das A, Plasmodium vivax malaria. *Emerg Infect Dis* 2005;11:132–134.
11. Mehta KS, Halankar AR, Makwana PD, Torane PP, Shah VB, Severe acute renal failure in malaria. *J Postgrad Med* 2001;47:24–26.
12. Prakash J, Singh AK, Kumar NS, Saxena RK, Acute renal failure in Plasmodium vivax malaria. *JAPI* 2003;51:265–267.
13. Dondorp AM, Lee SJ, Faiz MA, et al. The Relationship between Age and the Manifestations of and Mortality Associated with Severe Malaria; Oxford Journals, *Medicine, Clinical Infectious Diseases* 2006;47:151-157.
14. Ozen M, Gungor S, Atambay M, Dalal N. Cerebral malaria owing to Plasmodium vivax: case report. *Ann Trop Paediatr* 2009;26:141–144.
15. Krishna S, Waller DW, ter Kuile F et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. *Trans R Soc Trop Med Hyg* 1994;88:67-73.