

# Outcome analysis of patients presenting with neurological manifestations of Plasmodium Vivax malaria in tertiary care hospital of Mumbai

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## Abstract

**Objective:** *Plasmodium vivax* (*P. vivax*) infection has been considered for a long time a benign and self-limited disease. Percentage of complicated cases of vivax malaria is on the increasing trend, cerebral malaria being the most dreaded and a potentially life-threatening complication. **Material and Methods:** A prospective observational study was done after institutional ethics committee approval from July 2011 to February 2012 at tertiary care hospital in Mumbai. We studied the clinical profile and outcome of all the 48 patients above the age of 12 years diagnosed with Cerebral Malaria. **Results:** Incidence of neurological manifestations of vivax malaria in our hospital was 14.15%, with 32 (66.7%) out of 48 patients being males. The mean age of patients with neurological manifestations of vivax malaria was 29.66 years in discharged patients and 50.88 years in expired patients. Altered sensorium 37 (77.1%) followed by convulsion 28 (58.3%) were common findings, but focal neurological deficit, Bell's palsy, ataxia, psychosis were also seen. Mortality was higher (62.5%) in patients with premorbid conditions (p value <0.05) and that of with other system involvements (87.5%) including hepatic, renal, hepatorenal, pulmonary involvement (p value <0.05). Association between outcome with older age & high parasite index patients is significant (p value <0.001), however no such significant association was found in terms of gender distribution. **Conclusion:** *Plasmodium vivax*, as has been traditionally believed, is no longer a benign species and is causing presentations akin to *P. falciparum*. It is imperative that clinicians are aware of and ready to handle the complications caused by *Plasmodium vivax*.

**Keywords:** Plasmodium vivax, Neurological manifestation, Outcome

## Introduction

*Plasmodium vivax* (*P. vivax*) infection has been considered for a long time a benign and self-limited disease. However, with implementation of molecular diagnosis, it has become evident that *P. vivax* monoinfection could also be involved in multiple organ dysfunction and severe life-threatening disease as seen in *P. falciparum* infection [1,2]. Historically, cases of complicated *P. vivax* malaria have been rare and documented almost exclusively by case reports or small case series. Increasing resistance to chloroquine and

commonly used antimalarials in *P. vivax* parasites and the recent reports of involvement of this species in complicated malaria suggests the need for further research in vivax malaria. Neurological manifestations of malaria by convention refers to falciparum malaria, but vivax malaria being more common, the percentage of neurological manifestations of vivax malaria cases is on the increasing trend. Cerebral malaria is the most dreaded and a potentially life-threatening complication. Cerebellar ataxia, extra pyramidal rigidity and various psychiatric symptoms have been described either as the early manifestations of cerebral malaria or as a part of the post malaria neurological syndrome [3]. The

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incidence of malaria in Mumbai is rising because of various factors like overpopulation, lack of cleanliness, construction works, water stagnation, migrant workers, insecticide resistance, and antimalarial drug resistance [4].

This study intend to highlight the increasing incidence of neurological manifestations of vivax malaria and hence of the urgency of diagnosing and treating vivax malaria and not treating it as a benign disease. In the Indian scenario, these patients would initially be treated by the primary and the secondary care physicians. For the same reason, these physicians should be aware of the complications, so that earlier and effective treatment can be initiated and patients who need a referral to a tertiary care can also be identified.

**Methodology**

**Study Design:** A prospective observational study was carried out over 48 subjects after institutional ethics committee approval from July 2011 to February 2012 at tertiary care hospital in Mumbai.

**Inclusion Criteria**

- All the patients above the age of 12 years admitted with neurological manifestations with peripheral smear or Optimal positive for Plasmodium vivax.

**Results and Analysis**

Total number of indoor patients of vivax malaria (July 2011-February 2012) in our hospital was 339 out of them 48 patients had neurological manifestations with incidence of 14.15%. 32(66.7%) out of 48 patients were males and 16(33.3%) were female. Neurological manifestations in vivax malaria was common in 21–30 years (43.7%), followed by less than 20 years & more than 50 years (16.7% respectively). Maximum cases of neurological manifestations of vivax malaria were found in September (37.5%) month followed by October (20.8%). Altered sensorium 37(77.1%) followed by convulsion 28(58.3%) were common finding in neurological manifestations of vivax malaria, but focal neurological deficit, bell’s palsy, ataxia, psychosis were also seen (Table1). The co-morbid conditions like hypertension, diabetes mellitus, alcoholism, smoking, ischemic heart disease, observed in patients with neurological manifestations of vivax malaria. Association between pre-morbid conditions & outcome was statistically significant (P<0.05). Mortality was increased in patients with premorbid conditions.

- Those who are willing to give consent.

**Exclusion Criteria**

- Patients with mixed malaria,
- Co-existent leptospirosis and/or dengue.

Detailed history, clinical examination findings were noted and routine hematological, biochemical investigations carried out by treating physician were entered in case record form. We further studied the clinical profile and outcome of these patients.

**Statistical method:** ‘Paired t test’ was applied for comparison of variables like age, hemoglobin, platelet count, parasitic index. Chi-square test was used for comparing proportions. The p value less than 0.05 is considered statistically significant.

**Definition:** Neurological manifestations of plasmodium vivax malaria by definition refers to presence of high grade fever with altered Sensorium, generalized tonic clonic or partial convulsion when other metabolic & structural causes have been ruled out, cranial nerve palsy or demylnation, ataxia, psychosis, hemiplegia.

**Table 1: Neurological manifestations of P. Vivax malaria.**

Type of Presentation	Frequency	Percent
Altered Sensorium	37	77.1
Convulsion	28	58.3
Focal Neurological Deficit	7	14.6
Bell’s palsy	1	2.1
Ataxia	2	4.2
Psychosis	1	2.1

Out of 48 patients admitted 40 were discharged and 8 patients succumbed. 5 of expired patients were of age >50 years which was statistically significant with p value of 0.003. 5 out of 8 patients died were male and 3 were female (P value 1.00, not significant).33(82.5%) out of 40 discharged patients had isolated neurological involvement while 7(87.5%) out of 8 expired patients had neurological with other organ involvement. Association of isolated neurological manifestations of vivax malaria and that of with other system involvements including hepatic, renal, hepatorenal, pulmonary involvement was statistically significant in terms of outcome of disease (p value < 0.001). Thrombocytopenia was the most common finding in neurological manifestations of vivax malaria. Bleeding due to thrombocytopenia was seen in the form of epistaxis, melena, petechiae, ecchymoses, hematuria, subdural hematoma all necessitating platelet transfusions. The association of thrombocytopenia & outcome showed all 8 (100%) expired cases & 35 (87.5%) discharged were having thrombocytopenia. This association however was statistically not significant. Hepatic involvement was seen in 29.2% and renal failure was seen in 12.5% of patients with neurological manifestations of vivax malaria.

The association between hepatic involvement & outcome was statistically significant (P<0.037), neurological manifestations of vivax malaria with hepatic involvement related mortality was seen in 5 cases out of 8. The association between renal involvement & outcome was statistically significant (P<0.001), neurological manifestations of vivax malaria with renal involvement mortality was seen in 5 (62.5%) cases out of 8. We found 5(10.4%) patients with neurological manifestations of vivax malaria with pulmonary involvement, out of which 4(50%) succumbed to death and association was statistically significant (p value 0.005) (Table 2).

**Table-2: Association between organ involvement & outcome in P Vivax malaria with neurological involvement (N=48).**

Outcome		Hepatic		Renal		Pulmonary		Total
		Increased	Normal	Increased	Normal	Present	Absent	
Discharge	Count	9	31	1	39	1	39	40
	Percent	22.5%	77.5%	2.5%	97.5%	2.5%	97.5%	100%
Expired	Count	5	3	5	3	4	4	8
	Percent	62.5%	37.5%	62.5%	37.5%	50.0%	50.0%	100%
Total	Count	14	34	6	42	5	43	48
	Percent	29.2%	70.8%	12.5%	87.5%	10.4%	89.6%	100%
Fisher's Exact Test	P value	0.037		0.001		0.005		

**Table-3: Age, hemoglobin, platelet count, parasite index comparison in neurological manifestations of vivax malaria.**

Group Statistics	Outcome	No. of patients	Mean	Unpaired T test	P value
Age	Discharge	40	29.66	3.96	0.00
	Expired	8	50.88	Difference is significant	
Haemoglobin	Discharge	40	10.87	1.88	0.07
	Expired	8	9.10	Difference is not significant	
Platelets	Discharge	40	83,500.00	1.54	0.13
	Expired	8	52,500.00	Difference is not significant	
Parasite index	Discharge	40	2.43	10.56	0.00
	Expired	8	11.88	Difference is significant	

**Table-4: Association between parasite index & outcome in neurological manifestations of vivax malaria.**

Parasite Index		Outcome		Total
		Discharge	Expired	
Less than 5%	Count	35	1	36
	Percent	97.22%	2.77%	100.0%
5 to 10%	Count	5	1	6
	Percent	83.3%	16.7%	100.0%
More than 10%	Count	0	6	6
	Percent	0.0%	100.0%	100.0%
Total	Count	40	8	48
	Percent	83.33%	16.66%	100.0%
Chi-Square Tests	Value	df	P value	Association is
Pearson Chi-Square	31.106	2	0.000	Significant

We compared neurological manifestations of vivax malaria with respect to variables like age, sex, hemoglobin, parasitic index (PI), and platelet count (Table 3). The mean age of patients with neurological manifestations of vivax malaria was 29.66 years in discharged patients and 50.88 years in expired patients. No significant difference found in hemoglobin and platelets counts but parasite index was higher in expired patients. Thus outcome in older age & high parasite index patients is poor; however no such significant association was found in terms of gender distribution. Association between parasite index & outcome is statistically significant, hence high parasite index is suggestive of poor prognosis in patients with neurological manifestations of vivax malaria (Table 4). Association among focal neurological deficit and parasite index is however statistically not significance, hence parasite index is not associated degree of neurological deficit, in vivax malaria.

**Discussion**

Neurological manifestations of malaria is usually caused by *P. falciparum* but it has been observed that *P. vivax* malaria, which was otherwise considered to be benign malaria, with a low case-fatality ratio, is now increasingly associated with severe disease, including neurological manifestations, as with *P.falciparum malaria*. In our prospective observational study, we recruited 48 patients fulfilling the criteria for neurological manifestations of vivax malaria during the study period (July 2011-Feb 2012).

**Demographic profile in patients with neurological manifestations of vivax malaria:** The age profile of patients admitted with neurological manifestations of vivax malaria in our study depicts that most of the admitted patients (43.7%) were in the age group of 21-30 years. The findings observed in our study match with those observed in a retrospective study done in South Canara aimed at studying the demographic profile of malaria. Many of the patients were between the age group of 15 and 40 years, with high incidence between the age group of 21 and 30 years [5]. 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. Additionally city laborers from outstation stay in shanties with high vector population. The pattern observed in vivax malarial deaths was different as compared to those who survived. The peak of vivax deaths was observed in the age group >50 years (62.5%). 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 [6,7]. This explains the higher proportion of mortality observed in older age groups in our study.

Males outnumbered females in number of admissions as well as deaths. The findings in our study are supported by a similar finding highlighting the burden of malaria in India [8]. The deaths are more in men than women across all ages, whereas middle productive ages in general have much higher mortality than children. The reason for male dominance is that male subjects have more outdoor work and more prone to vector bite.

**Clinical profile of patients with neurological manifestations of vivax malaria:** Altered sensorium 37 cases (77.1%) followed by convulsion 28 cases (58.3%) are common manifestations and focal neurological deficit 7 cases (14.5%), ataxia 2 cases (4.2%), bell's palsy 1 case (2.1%), psychosis 1 case (2.1%) was also found (Table 1). Three cases of *Plasmodium vivax* malaria (all adult male patients) complicated by seizures and symptoms of diffuse meningoencephalitis were reported by Sarkar et al [9]. Out of 12 cases of cerebral involvement due to vivax malaria reported by Nadkar et al 3 had multiple convulsions; 5 had impaired consciousness and 4 had deep coma [7]. Published reports by various authors have found presentations ranging from seizures, decreased level of consciousness, aphasia, hemiparesis, delirium, coma, stupor, psychosis associated with *Plasmodium vivax* [10, 11].

**Outcome analysis of patients with neurological manifestations of vivax malaria:** Thrombocytopenia was the most common finding in neurological manifestations of vivax malaria with all expired 8 (100%) & many discharged 35 (87.5%) subjects were having thrombocytopenia. One such study was done in Karachi among 124 patients of Malaria Parasite positive, frequency of thrombocytopenia was 71.87% (n=46) in falciparum and 93.33% (n=56) in vivax infection [12]. In another study by Patel P et al incidence of thrombocytopenia was seen in 83.80% and 74% cases of *P. falciparum* and *P. vivax* malaria respectively [13]. As shown in Table 2 hepatic involvement was seen in 29.2% and renal failure was seen in 12.5% of patients with neurological manifestations of vivax malaria in our study and association was statistically significant in terms of outcome of disease. 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 [14].

Thus hepatic dysfunction was the most common complication seen in severe vivax malaria in the study in Bikaner followed by renal failure, which is comparable finding to our study. 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 favorable [15]. However in our study we observed that ARF when associated with neurological involvement has poor outcome.

When we studied neurological manifestations of vivax malaria with respect to variables like hemoglobin, parasitic index, and platelet count; no significant difference found in hemoglobin and platelets counts but parasite index was higher in expired patients. Higher parasite index associated with high grade of altered sensorium, while association between parasite index and convulsion or focal neurological deficit is statistically not significant. In study by Kulkarni VK et al PI of >5% was observed in 63 patients in *falciparum* group as compared to 27 patients from *vivax* group [16]. Only 3 patients with PI of <5% died whereas 19 patients with PI of >5% died from both the groups. Higher PI was associated with more mortality and this finding was statistically significant.

**Limitations of our study:** This study was conducted in a tertiary care hospital in a metropolitan city; hence the observation and conclusions of this study cannot be extrapolated to the general population, especially those from rural areas. Also in view of small sample size more studies with larger number of subjects needed to confirm findings. However, this study will help to form the basis for similar studies in the future.

## Conclusion

The highest incidence of neurological manifestations of vivax malaria was seen in males and in the age group of 21-30 years; whereas maximum deaths were seen in the age group of >50 years. Mortality was higher (62.5%) in patients of neurological manifestations of vivax malaria with pre-morbid conditions and that of with other system involvements (87.5%) including hepatic, renal, hepatorenal, pulmonary involvement and also high PI of > 5%.

Thus, *Plasmodium vivax*, as has been traditionally believed, is no longer a benign species and is causing presentations akin to *P. falciparum*. It is imperative that clinicians are aware and are ready to handle the complications caused by *Plasmodium vivax* which have been traditionally associated with *P. falciparum* malaria. The key to management is early diagnosis and initiation of treatment based on a high index of suspicion.

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