J R Coll Physicians Edinb 2018; 48: 198–201 | doi: 10.4997/JRCPE.2018.302 ORIGINAL RESEARCH PAPER

Neurological complications in patients with *Plasmodium vivax* malaria from Karachi, Pakistan

A Akhlaq[1], NK Ghanchi[2], B Usmani[3], R Shahzad[4], A Rahim[5], M Wasay[6], MA Beg[7]

Abstract

Background Malaria remains an endemic disease in Pakistan with an estimated healthcare burden of 1.6 million cases annually, with *Plasmodium vivax* accounting for 67% of reported cases. *P. vivax* is the most common species causing malaria outside of Africa, with approximately 13.8 million reported cases worldwide.

Method We report a series of *P. vivax* cases with cerebral involvement that presented at Aga Khan University Hospital, Karachi, Pakistan.

Results The majority of the patients presented with high-grade fever accompanied by projectile vomiting and abnormal behaviour, seizures, shock and unconsciousness. Seven of 801 patients with *P. vivax* monoinfection presented or developed cerebral complications. *P. vivax* infections were diagnosed based on peripheral smears and rapid diagnostic testing.

Conclusion *P. vivax* infection can lead to severe complications, although not with the frequency of *Plasmodium falciparum* infection. Current cases highlight an increasing trend of cerebral complications caused by *P. vivax*.

Keywords: cerebral complications, malaria, *Plasmodium vivax*, seizure

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Correspondence to:
MA Beg
Department of Pathology and Laboratory Medicine
Aga Khan University
Karachi PO 3500
Pakistan

Email:
masim.beg@aku.edu

Introduction

Malaria is a global public health issue. It is a major cause of death from infectious disease with more than 212 million clinical cases annually and an estimated 429,000 deaths being reported worldwide. Owing to the various measures implemented to reduce the spread of malaria, the incidence of malaria has been reduced by 41% worldwide and malaria-related deaths have reduced nearly 62% between 2000 and 2015. However, approximately 3.2 billion people are still at risk of developing malaria. In 2015, the number of confirmed malaria cases reported in Pakistan was 202,013.[1] Overall, the prevalence of *Plasmodium vivax* compared to *Plasmodium falciparum* has increased over the past few years in Pakistan.[2] Pakistan reported 10% of the total worldwide cases of *P. vivax* in 2015, and 11% of worldwide deaths due to *P. vivax*.

P. falciparum is most common in Africa, while *P. vivax* is more prevalent worldwide. In Pakistan, *P. vivax* contributes to 85% cases, while *P. falciparum* accounts for 15%.[1] Infection with *P. falciparum* is associated with a higher complication rate than any other type of *Plasmodium* infection. Complications associated with *P. falciparum* include severe anaemia, respiratory distress syndrome, hypoglycaemia, acidosis and renal failure, as well as cerebral malaria, convulsions and shock.[3,4] Severe anaemia and hypoglycaemia occur more commonly in children; while respiratory oedema, renal failure and jaundice are common in adults. Coma and acidosis occur in all age groups.[4]

Although highly prevalent, *P. vivax* has always been associated with increased morbidity but reduced mortality compared to its human malarial counterpart *P. falciparum*.[5] However, recent studies from Indonesia, Papua New Guinea, Thailand, Brazil, India, Iran and Pakistan have shown that *P. vivax*, either independently or in synergy with comorbidities/mixed plasmodia species, can cause severe or even fatal malaria episodes.[2,6–9] Several cases of severe malaria due to *P. vivax* have been reported in past decades. Complications reported with monoinfection of *P. vivax* include acute pulmonary oedema, severe anaemia, coma, respiratory distress, severe jaundice, renal failure haemodynamic shock and thrombocytopenia.[6,7,10] Risk factors associated with severe malaria are young children (under 5 years), pregnancy and lack of immunity.

P. falciparum is known for severe neurological complications and is a known cause of cerebral malaria. The mechanism of cerebral malaria in *P. falciparum* is associated with

[1,3]MD, Medical College, Aga Khan University Hospital, Karachi, Pakistan; [2]Assistant Professor, [4]MD, [5]Statistician, [7]Consultant and Professor, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi, Pakistan; [6]Consultant and Professor, Section of Neurology, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan

microvascular occlusion, red blood cell sequestration and impaired perfusion due to parasitised red blood cells. There is also an increase in blood–brain barrier permeability, oedema and a mild leukocytic response.[8]

Neurological complications associated with *P. vivax* reported previously include thalamic bleeds, acute disseminated encephalomyelitis, acute subdural haematomas, bilateral facial palsies and facial diplegia.[9,11–15] Cerebral malaria due to *P. vivax* has been reported in children.[16]

We report neurological complications in patients infected with *P. vivax* in our setting. Predictive and prognostic indicators for the development of neurological complications in a patient with *P. vivax* infection were also observed.

Methods

A retrospective study was conducted at the Aga Khan University Hospital, Karachi, Pakistan, and included review of charts from patients with *P. vivax* malaria enrolled over 6 years (2009–14). The study subjects were patients who presented with *P. vivax* monoinfection or mixed infection of *P. vivax* and *P. falciparum* (mixed). Inclusion criteria for the study were adults (≥18 years) with microscopy-confirmed *P. vivax* monoinfection. Patients infected with *P. falciparum* monoinfection were excluded. Patients with known haematological malignancies, chronic liver disease or hyperspleenism due to other causes were also excluded. Clinical syndromes were classified as severe on the basis of the World Health Organization's 2010 severe *P. falciparum* malaria criteria with the exclusion of parasite density thresholds.[17]

Patients were further stratified based on neurological complications, including seizures, altered mental status, coma, headaches, psychosis, agitation, prostration, focal deficits, loss of consciousness, loss of reflexes and ocular complications, observed within the course of disease or on follow up.

The data were analysed using SPSS 22. Descriptive statistics were calculated. The baseline characteristics of the study population with haematological parameters were calculated as mean ± standard deviation. Categorical variable was computed as frequency and percentages. To compare the *P. vivax* and mixed infections among different categorical variables appropriate chi-squared or Fisher exact tests were applied. Kaplan–Meier test methods were applied by using proportion cumulative survival function on the basis of log-rank test methods. p-value <0.05 was considered significant.

Results

Of 801 patients included in the study, 715 presented with *P. vivax* and 86 with mixed infections. Seven patients with *P. vivax* monoinfection developed neurological symptoms. One patient had a relapse of *P. vivax* and presented with mixed infection during the relapse. Confirmation of malaria infection was based on blood film microscopy and rapid diagnostic test (immunochromatographic test malaria). The mean patient age was 44 years, range: 19–75 years. Interestingly, the patients who developed neurological symptoms were male.

Patients with neurological complication had pre-existing comorbidities, such as hypertension, epilepsy, diabetes mellitus type II or cardiovascular disease, among others. Presenting symptoms in patients with monoinfection *P. vivax*, haematological parameters and gender associations to neurological complications are compared in Table 1.

We compared several presenting complaints, including uncontrolled movements, seizure, rash, paresis/paralysis, loss of consciousness, vomiting and fever in patients with *P. vivax* infection. All patients with mixed infections presented with mostly non-specific symptoms, with loss of appetite being common in mixed malaria patients, but not in patients with *P. vivax*.

Physical examination of the patients with *P. vivax* monoinfection at the time of admission showed normal neurological function that deteriorated later during admission. MRI findings observed in *P. vivax*-positive patients who developed neurological complications were cortical infarcts, cerebral oedema, basilar haemorrhage and frontoparietal haemorrhage to ex-vacuo lateral ventricle dilation.

Mean platelet count in patients with malaria was 50.44 x 10^4 platelets, with a lower count in *P. vivax* monoinfection patients. Prothrombin time was found to be significantly lower in patients with *P. vivax* monoinfection (11.63 ± 1.16 s) than with mixed infection (20.70 ± 6.08 s; p-value: 0.006).

Treatment of patients infected with *P. vivax* only comprised artemether alone (22.2%), chloroquine alone (22.2%) and artemether in combination with chloroquine (33.3%). The average hospital stay was 6.2 days (standard deviation: 9.48 days; range: 1–30 days). The median hospital stay was calculated (to eliminate the one extreme value of 30 days) as 3 days.

All seven patients with neurological complaints survived without any residual symptoms. One patient died (11.1%) from the course of disease. Mixed malaria infection was associated with poorer outcomes and a higher rate of deterioration (Figure 1). The type of malaria or the outcome (alive vs dead) was not found to have any significant association to the duration of stay at the hospital.

Further analysis revealed no relationship between associated comorbidities and patient outcome, or between various presenting complaints and patient outcome. Although most patients with malaria presented with normal neurological exam, upgoing planters response was seen with poorer outcomes.

Discussion

Our results revealed male gender to be a predisposing factor for the development of neurological complications in

Table 1 Clinical features of patients with severe *Plasmodium vivax* infection from Karachi, Pakistan

Characteristic	No. patients with *P. vivax* monoinfection							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**Descriptive statistics***
Age (year)	44	35	54	19	34	75	54	Mean ± SD: 31.0 ± 15.33
Duration of illness (hospital stay in days)	4	3	2	2	1	8	4	Mean ± SD: 2.5 ± 1.19
Fever	+	+	+	+	+	+	+	Present in 7/7 (100%)
Seizures	–	+	+	–	–	–	+	Present in 3/7 (42%)
Vomiting	+	–	–	+	–	+	–	Present in 3/7 (42%)
Drowsiness	–	–	–	–	+	+	–	Present in 2/7 (28%)
Malaise	+	–	–	+	–	–	–	Present in 2/7 (28%)
Paresis	–	–	–	–	+	–	–	Present in 1/7 (14%)
Loss of consciousness	–	–	+	–	–	+	–	Present in 2/7 (28%)
Extensor planter reflex	–	–	–	–	+	–	+	Present in 2/7 (28%)
Uncontrolled hand movements	+	–	–	–	–	–	–	Present in 1/7 (14%)
Haematological parameters								
Haemoglobin (gm/dl)	11.1	9.8	13.5	11	14.1	8.1	13.5	Mean ± SD: 11.5 ± 2.2
Prothrombin time (s)	12.5	13.4	10.9	10.6	10.6	12.6	11.7	Mean ± SD: 11.6 ± 1.2
Haematocrit (%)	33	28	38	31.7	41	23.5	38.2	Mean ± SD: 33 ± 6
Platelets (10^9/l)	30	72	96	17	17	71	17	Mean ± SD: 45 ± 33
Serum creatinine (mg/dl)	1.4	0.4	1.10	1	0.9	1.4	1.2	Mean ± SD: 1.05 ± 0.3
Malaria treatment								
	AT	CQ, AT	AT	CQ	AT, CQ	CQ, AT	CQ	

All patients were male.
*Statistics derived in SPSS software version 22.
+, present; AT, atemether oral; CQ, chloroquine; SD, standard deviation

patients with *P. vivax*. Few cases address female patients developing neurological complications. The average patient age was 44 years. Neurological complications in *P. vivax* have been reported in the paediatric age group.[16] Several cases reported from neighbouring India involving neurological complications in adults with *P. vivax* concur with data reported in this study.[9,11,12,14,15]

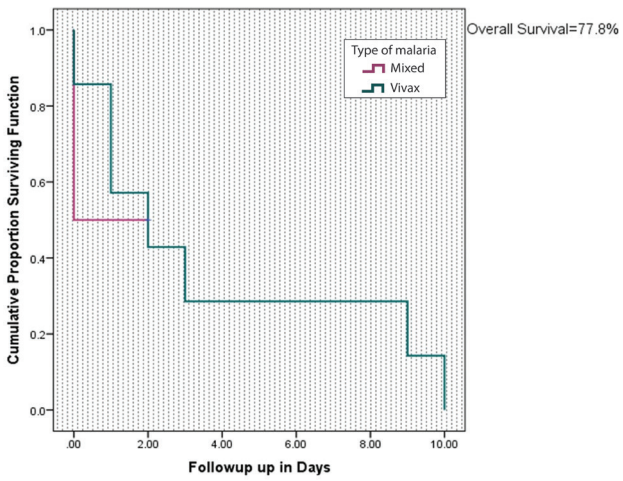

Figure 1 Survival in patients with *Plasmodium vivax* and mixed infection that developed neurological complications. Survival curves were generated by applying Kaplan–Meier test method using proportion cumulative survival function on the basis of log-rank test methods

Patients with mixed infection of *P. falciparum* and *P. vivax* presented with symptoms non-specific for neurological complications, with loss of appetite being common. However, patients with *P. vivax* monoinfection presented with symptoms more specific for neurological involvement, including drowsiness, paresis, uncontrolled hand movements, loss of consciousness and seizures.

Patients with *P. vivax* monoinfection presented with normal neurological examinations at the time of admission but later developed neurological complications, such as extensor planter reflex (Babinski response). Previous studies have revealed coma to be the most significant prognostic factor in terms of patient mortality associated with severe malaria in *P. falciparum*.[4] This finding is consistent with our study in which drowsiness with associated upgoing planters response and was related to mortality.

Thrombocytopenia observed in this study was more severe in *P. vivax* monoinfection than in mixed infections. Severe

thrombocytopenia has been associated with *P. vivax* patients.[6]

Patients with *P. vivax* monoinfection presented with lower platelet counts than those with mixed infection, which concurs with previous studies.[2] However, this finding is in contrast to previous studies that indicate *P. falciparum* attenuates the intensity of *P. vivax* infection.[18] Yet, prothrombin time was higher with mixed infections than *P. vivax* monoinfection.

Cortical infarcts, cerebral oedema, basilar hemorrhage, frontoparietal haemorrhage and ex-vacuo lateral ventricle dilation were seen on MRI. Previous reports have shown that cerebral malaria is most commonly associated with the paediatric age group.[19] Mixed infections are associated with higher mortality and a higher rate of deterioration.[5]

Multiorgan dysfunction observed during severe malaria is associated with a systemic inflammatory response triggered by, among other factors, leukocyte adhesion to organ microvasculature, parasitised erythrocytes and production of inflammatory mediator. Multiorgan dysfunction has been reported in India and Brazil and found to be associated with poor outcomes in severe *P. vivax* malaria cases.[20,21]

P. vivax is a major contributor to the disease effects of malaria, including severe malaria, in a tertiary care setting in Karachi, Pakistan. Furthermore, *P. falciparum* and *P. vivax* have similar rates for several complications (pulmonary oedema, metabolic acidosis, abnormal bleeding, renal impairment and death). Severe malaria with cerebral complications due to *P. vivax* would place an additional burden on a weak healthcare system leading to increased morbidity and mortality.

Safety practices to avoid exposure are the primary prevention method. Immediate reporting of suspected exposures is important to initiate prompt evaluation and treatment, if needed. Recommended prophylaxis for *P. vivax* high endemic areas are chloroquine (two tablets weekly 155 mg) plus proguanil (two tablets daily 100 mg).[22] Effective chemoprophylaxis taken correctly should reduce the risk of malaria by around 90%, especially if combined with sleeping under insecticide-treated nets.

References

1 World Health Organization. *World Malaria Report (2008–2016).* Geneva: World Health Organization; 2016.
2 Zubairi ABS, Nizami S, Raza A et al. Severe *Plasmodium vivax* malaria in Pakistan. *Emerg Infect Dis* 2013; 19: 1851–4.
3 White NJ, Pukrittayakamee S, Hien TT et al. Malaria. *Lancet* 2014; 383: 723–35.
4 Dondorp AM, Lee SJ, Faiz MA et al. The relationship between age and the manifestations of and mortality associated with severe malaria. *Clin Infect Dis* 2008; 47: 151–7.
5 Anstey NM, Russell B, Yeo TW et al. The pathophysiology of vivax malaria. *Trends Parasitol* 2009; 25: 220–7.
6 Rahimi BA, Thakkinstian A, White NJ et al. Severe vivax malaria: a systematic review and meta-analysis of clinical studies since 1900. *Malar J* 2014; 13: 481.
7 Manning L, Laman M, Law I et al. Features and prognosis of severe malaria caused by *Plasmodium falciparum*, *Plasmodium vivax* and mixed *Plasmodium* species in Papua New Guinean children. *PLoS One* 2011; 6: e29203.
8 Idro R, Jenkins NE, Newton CR. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. *Lancet Neurol* 2005; 4: 827–40.
9 Kochar DK, Sirohi P, Kochar SK et al. Post-malaria neurological syndrome – a case of bilateral facial palsy after *Plasmodium vivax* malaria. *J Vector Borne Dis* 2007; 44: 227–9.
10 White NJ. Determinants of relapse periodicity in *Plasmodium vivax* malaria. *Malar J* 2011; 10: 297.
11 Sarkar J, Naik B, Gawande A et al. Vivax malaria: a rare cause of thalamic bleed. *Asian Pac J Trop Med* 2012; 5: 665–6.
12 Koibuchi T, Nakamura T, Miura T et al. Acute disseminated encephalomyelitis following *Plasmodium vivax* malaria. *J Infect Chemother* 2003; 9: 254–6.
13 Ghosh S. Curious association between *Plasmodium vivax* malaria and nontraumatic acute subdural hematoma. *Indian J Crit Care Med* 2014; 18: 335–6.
14 Venugopal V, Haider M. First case report of acute hemorrhagic leukoencephalitis following *Plasmodium vivax* infection. *Indian J Med Microbiol* 2013; 31: 79–81.
15 Sim JE, Choi YC, Kim WJ. Facial diplegia in *Plasmodium vivax* malaria. *J Clin Neurol* 2010; 6: 102–3.
16 Tanwar GS, Khatri PC, Sengar GS et al. Clinical profiles of 13 children with *Plasmodium vivax* cerebral malaria. *Ann Trop Paediatr* 2011; 31: 351–6.
17 World Health Organization. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: World Health Organization; 2010.
18 Luxemburger C, Ricci F, Nosten F et al. The epidemiology of severe malaria in an area of low transmission in Thailand. *Trans R Soc Trop Med Hyg* 1997; 91: 256–62.
19 Ozen M, Gungor S, Atambay M et al. Cerebral malaria owing to *Plasmodium vivax*: case report. *Ann Trop Paediatr* 2006; 26: 141–4.
20 Patil DR, Nikumbh SD, Parulekar A et al. Multiorgan dysfunction in *Plasmodium vivax* malaria: a prospective study. *Int J Sci Stud* 2015; 3: 155–62.
21 Costa FT, Lopes SC, Albrecht L et al. On the pathogenesis of *Plasmodium vivax* malaria: perspectives from the Brazilian field. *Int J Parasitol* 2012; 42: 1099–105.
22 Chiodini PL, Field VK, Hill DR et al. *Guidelines for malaria prevention in travellers from the United Kingdom.* London: Public Health England; 2013.