J Vector Borne Dis 48, December 2011, pp. 219–223

A study on pulmonary manifestations in patients with malaria from north-western India (Bikaner)

K.C. Nayak, Mohini, S. Kumar, R.S. Tanwar, V. Kulkarni, A. Gupta, P. Sharma, P. Sirohi & P. Ratan

Department of Medicine, S.P. Medical College, Bikaner, Rajasthan, India

ABSTRACT

Background & objectives: Plasmodium falciparum (Pf) and *Plasmodium vivax (Pv)* are responsible for most of the global burden of malaria. With changing spectrum of clinical presentation in malaria, pulmonary system involvement has always been under diagnosed. The present study was planned to estimate the pulmonary system involvement in patients with malaria from north-western India (Bikaner).

Study design & description of the patients: Our study was conducted during 2007 to 2009 in 200 cases of severe malaria [*Pf* , *Pv,* and mixed (*Pf* + *Pv*)] with pulmonary involvement. It included adult patients of both sexes (145 males and 55 females) belonging to all age groups. The diagnosis of *Pf* and *Pv* was confirmed by demonstrating asexual form of parasites in peripheral blood smear and OptiMal test.

Main outcome measures: Pulmonary involvement was observed in 30% (60/200) patients among which cough in 24% , dyspnea in 12%, acute respiratory distress syndrome (ARDS) in 7% , bronchitis in 3% and pneumonia in 1.5% were the major clinical manifestations of malaria. Metabolic acidosis and low oxygen saturation was observed in 7% patients. Chest X-ray abnormality in 11.5% patients, 7% had bilateral infiltrates, 1.5% had inflammatory patch and 3% had findings suggestive of bronchitis. Spirometry findings showed 17% patients had early small airway obstruction. All the patients with ARDS had poor disease outcome.

Results & conclusion: Our results suggest that pulmonary system involvement was observed in patients infected with *Pf* and *Pv*. If these clinical presentations are ignored, it may lead to delay in diagnosis and can alter the outcome and prognosis of the disease. Therefore, early diagnosis of malaria induced ARDS can significantly affect the outcome.

Key words Bikaner; India; *Plasmodium falciparum; Plasmodium vivax;* pulmonary functions

INTRODUCTION

Plasmodium falciparum and *P. vivax* are responsible for most of the global burden of malaria. More than two billion people are at the risk of contracting malaria[1], especially in the tropical and subtropical countries. Recent epidemiologic models, geographical and demographic data suggest that in India about two million confirmed cases and 1000 deaths are reported annually, although 15 million cases and 20,000 deaths are estimated by WHO-South East Asia Regional Office (SEARO), India. In the South-eastern Asian Region of WHO, of ~1.4 billion people living in 11 countries (land area, 8,466,600 km^2; i.e. 6% of global area), 1.2 billion are exposed to the risk of malaria, most of whom live in India. However, Southeast Asia contributed to only 2.5 million cases to the global burden of malaria. Of this, India alone contributed 76% of total cases[2].

Usually patients with uncomplicated malaria present with fever and non-specific symptoms, complicated and severe malaria can cause multiorgan involvement including acute respiratory distress syndrome (ARDS)[3]. The spectrum of severe malaria has changed worldwide as well as in India[4]. Important clinical features include acute non-cardiogenic pulmonary edema, ARDS, acute lung injury (ALI) and intestinal pneumonia. Anstey *et al*[5] demonstrated that clinically uncomplicated cases of both *P. falciparum* and *P. vivax* malaria presented with compromised pulmonary functions including small airway obstruction, gas exchange alterations and increased pulmonary phagocytic activity. Maguire *et al*[6] observed that in uncomplicated and severe *P. falciparum* malaria, pulmonary vascular occlusion occurs. However, impaired alveolar-capillary membrane functions were seen in patients with severe malaria. In contrast to falciparum malaria, vivax malaria is rarely associated with serious complications. It was presumed that *P. vivax* infection may lead to severe consequences only when possibility of mixed infections exists[7] and the pulmonary manifestations were so far under-diagnosed. ARDS was observed as have drastic onset in pa-

tients infected with *P. vivax* malaria and required immediate life-support[4].

Bikaner district is a part of the Thar Desert, India having extremes of temperature. This region has always been regarded as hypoendemic area for malaria. This is basically an arid zone, which had recently experienced changes in ecosystem due to increased rainfall and canal irrigation in the last two decades. The scenario of both disease morbidity and mortality has altered to a great extent during the past decades. Reports of malaria cases in 1995 showed that 3.18% of total malaria cases and 0.28% of total *P. falciparum* cases were reported from Rajasthan (Source: NVBDCP). There are increasing reports of multiple organ dysfunctions and severe pulmonary syndrome in falciparum malaria[3,8]. However, meagre reports have been found for pulmonary manifestation in *P. vivax* infected patients[4,9,10]. Therefore, the aim of the present clinico-epidemiological study was to assess the incidence, clinical profile and outcome for respiratory system manifestation of malaria.

MATERIAL & METHODS

Patients and study site

This study was conducted on 200 patients with malaria. The cases were selected randomly amongst all the patients of malaria admitted other than those in exclusion criteria. The patients of both sexes were irrespective of age, except the pediatric age group. The diagnosis of malaria was confirmed by examination of thick and thin smear/OptiMal test. Only those cases with asexual forms of *Plasmodium* in the blood by smear examination or found positive in OptiMal test 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 (because the parasites are numerous there) and a minimum of 100 fields were examined before declaring the slides negative for *Plasmodium*. The patients with any other systemic disease, chronic respiratory disease, chronic obstructive pulmonary disease, bronchitis, and pulmonary tuberculosis were excluded from study. Smokers, pregnant or lactating females and those unable to give informed consent were also excluded.

Clinical and pulmonary function assessment

Clinical history for all patients was properly taken. All patients underwent detailed laboratory investigation, which included hemoglobin, total and differential leukocyte count, platelet count, serum bilirubin, serum asparate aminotransferase and alanine aminotransferase, blood sugar, serum creatinine, blood urea, serum electrolyte, complete urine examination. ECG, X-ray chest, ultrasound abdomen, pulse oxymetry, blood gas analysis and pulmonary function tests were done in selected patients.

All patients received uniform drug regimen in the form of either artesunate 2.4 mg/kg over 10 min followed by 2.4 mg/kg every 24 h or I.V. quinine (20 mg/kg) loading dose over 4 h in Day 1 then 10 mg/kg at 8 hourly for a total of 7 days of therapy. Antibiotics were given in selected patients those who required. Oxygen therapy was given in patients who required. All the patients of ARDS were given ventilator support. Follow-up was done on Day 14.

Ethical approval and informed consent

The study was ethically approved by the institutional ethics committee within the framework of the larger project. Patients or patient's guardians were asked for written informed consent by the research nurse. Moreover, the procedure performed (systemic clinical examination and history, and diagnostic test for malaria) provided patients with a laboratory-confirmed diagnosis of malaria and consequently with better management of the disease.

RESULTS

The study was conducted on 200 adult malaria patients [Males = 145 (72.5%); Females = 55 (27.5%)] admitted during 2007–09. In our study, 80 (40%), 80 (40%) and 40 (20%) cases were infected with *P. falciparum*, *P. vivax*, and mixed infections (*Pf* + *Pv*), respectively. Distribution of malaria cases [*P. falciparum*, *P. vivax*, and mixed (*Pf* + *Pv*)] according to age showed that maximum patients 113 (56.5%) were in the age group of 21–40 yr. The minimum number of malaria cases 16 (8%) were in the age group >60 yr.

Respiratory system involvement was observed in 60 (30%) malaria patients. Of these, 43 (21.5%), 14 (7%), and 3 (1.5%) were infected with *P. falciparum*, *P. vivax*, and mixed infections (*Pf* + *Pv*), respectively. The different pulmonary manifestations are presented in Table 1. In patients with respiratory involvement, 48 (24%) malaria patients presented with cough, out of which 32 (16%) had dry cough. The majority 44 (22%) were infected by *P. falciparum* malaria, 3 with *P. vivax*. Respiratory rate of maximum patients (64%) ranged between 14 and 18 breaths/min. Fourteen (7%) patients had respiratory rate >25, out of which 9 were infected with *P. falciparum* malaria. Pneumonitis (as per WHO guidelines) was observed in 3 patients. Six patients had acute bronchitis, out of which 4 were of *P. falciparum* and 1 each for *P. vivax* and mixed

Table 1. Distribution of pulmonary manifestations (clinical and laboratory) in relation to patients of different types of malaria

Pulmonary manifestation	Types of malaria			Total No. (%)
	P. falciparum No. (%)	*P. vivax* No. (%)	Mixed infections (*Pf* + *Pv*) No. (%)	
Cough	44 (22)	3 (1.5)	1 (0.5)	48 (24)
Dyspnea	16 (8)	6 (3)	2 (1)	24 (12)
Bronchitis	4 (2)	1 (0.5)	1 (0.5)	6 (3)
Pneumonitis	2 (1)	1 (0.5)	0 (0)	3 (1.5)
ARDS	9 (4.5)	4 (2)	1 (0.5)	14 (7)
Small airway obstruction	16 (8)	10 (5)	8 (4)	34 (17)
ABG abnormality	10 (5)	3 (1.5)	1 (0.5)	14 (7)
Low oxygen saturation	9 (4.5)	4 (2)	1 (0.5)	14 (7)
Chest X-ray abnormality	15 (7.5)	5 (2.5)	3 (1.5)	23 (11.5)

Figures in parentheses indicate percentages.

infections (*Pf* + *Pv*). ARDS (as per WHO guidelines) was presented in 14 of malaria patients, out of which 9 were of *P. falciparum* and 4 were infected with *P. vivax*. Dyspnea was observed in 24 patients. Abnormal chest X-ray was presented in 23 patients infected with malaria. Fourteen had infiltrate, 3 had inflammatory patch and 6 had findings suggestive of bronchitis.

Early airway obstruction was observed in 34 cases as assessed by spirometry, out of which 16 were infected with *P. falciparum* and 10 with *P. vivax*. Ten patients showed reversibility after salbutamol (200 µg) inhalation after two minutes. Twenty-four patients showed no effect of medication. Repeating the spirometry after 14 days showed that 10 had persistence of early small airway obstruction. Metabolic acidosis was present in 14 malaria patients as assessed by blood gas analysis. Oxygen saturation in maximum 14 ranged between 96 and 100%.

Severe anaemia (haemoglobin < 5 mg%) was observed in 67 (33.5%), out of which 28 were infected with *P. falciparum*, 26 with *P. vivax*, and 13 were mixed infections (*Pf* + *Pv*). Total leukocyte count (TLC) in range of 4000–11000/µl was observed in 182 (91%) patients. Jaundice was present in 68 (29%), out of which 12% were *P. falciparum* and 10% were infected with *P. vivax* and 7% were mixed (*Pf* + *Pv*) infections. Eighteen patients had serum creatinine >3 mg/dl and 16 had blood urea around 100 mg/dl. Outcome of malaria patients with respiratory system involvement showed that 46 (23%) recovered and 14 (7%) expired.

DISCUSSION

With spurt in developmental activities in the Bikaner region (north-western India), marked changes in epidemiological and clinical profile of malaria over last few decades has been observed. Although pulmonary manifestation has invariably been reported in *P. falciparum* malaria but its association with *P. vivax* is also been noticed recently. In India, about 70% infections are reported due to *P. vivax*, 25.3% due to *P. falciparum* and 4–8% due to mixed infections. Although our study do not reflect the true prevalence of *P. falciparum* and *P. vivax* in the community as most of our patients were from Bikaner City, others were complicated cases referred from primary health centers situated in rural areas with semi developed medical facilities. In this study, 16.67% of total cases were from urban area of Bikaner and one fourth (25%) of cases were complicated and referred from primary health centers in Bikaner, which are the main pockets of existence of *P. falciparum* malaria.

Gozal[11]has conducted a study on 50 *P. falciparum* infected patients and dyspnea was observed in 2. Mishra & Ray[12] conducted a study on 150 cases in which 72 (48%) were *P. vivax*, 54 (36%) of *P. falciparum*, and 24 (16%) were mixed infections. Forty-five patients had respiratory symptom involvement and 40% of these have dyspnea, of these 45 patients 42 (93.4%) were of *P. falciparum* malaria. In a study done by Rajput *et al*[13] on 100 patients (53 *P. vivax*; 36 *P. falciparum* and 11 mixed infections), 26/100 had respiratory involvement. Incidence of dyspnea in our study was comparable to those observed by Mishra & Ray[12] and Rajput *et al*[13], however, we noticed an increased incidence of dyspnea in patients of *P. vivax*.

In recent years, incidence of pulmonary manifestation has increased in patients with malaria[11]. The present study results are in conformity with the findings of other studies by Anstey *et al*[5], Mishra & Ray[12], and Gozal[11], however, an increased incidence was observed in those

infected with *P. vivax*. We suggest increased incidence of pulmonary manifestation in recent decades.

We observed that 3 (1.5%) malaria patients presented with pneumonitis. The findings were in accordance with the incidence observed by Rajput *et al*[13] and Mishra & Ray[12]. Our patients presented with fever, chills and cough which was productive on examination. On sputum culture examination, this came out to be sterile. On examination wheeze was present on auscultation. Chest X-ray findings suggested of bronchitis. In all these patients, there was no previous history of any respiratory disease and the coughing coincides with onset of fever. Therefore, we concluded that *Plasmodium* itself is capable of causing pneumonia. Tong *et al*[14] and Applebaum *et al*[15] also suggested that pneumonia presented during malaria is directly contributed by the disease pathogen itself. Out of 60 patients with respiratory involvement, 6 (3%) presented with acute bronchitis. The previous study conducted by Mishra & Ray[12] and Rajput *et al*[13] also observed the same incidence.

ARDS was presented in 14 malaria patients. Our findings were comparatively higher than that seen in studies of Mishra & Ray[12] and Rajput *et al*[13] this may be due to larger sample size of our study. We observed that in patients of ARDS, 11 had bilirubin in range of 10–20 mg/dl. Eight had TLC >11000/µl. These patients present with abrupt onset of dyspnea, cough, and tightness of chest. On physical examination these patients presented with acute respiratory distress, expiratory wheeze and creptations. Cyanosis was also noticed. X-ray findings in these patients were suggestive of ARDS and O_2 saturation was quite low. Blood gas analysis done on these patients showed metabolic acidosis. All such patients were on antimalarials, antibiotics, and ventilator support was immediately provided. However, none of these patients survived. This showed that mortality rate in malaria ARDS is high and it can improve the outcome, if identified timely. Rajput *et al*[13] observed that ARDS was presented in 4 patients out of 29 with respiratory involvement. Mishra & Ray[12] observed ARDS in 7 cases out of 45 patients with respiratory involvement. Sarkar *et al*[4] reported three cases of sudden onset of ARDS from Kolkata as a complication of *P. vivax* malaria. Mohan *et al*[16] explained the pathogenesis of malaria ARDS to be due to erythrocyte sequestration and destruction, the release of parasite and erythrocyte material into the circulation, and host response to these events. Ventilation perfusion mismatch and defect are most likely functional explanation. Heavy intravascular monocytic infiltrates provoking inflammatory lesions to the endothelium of the lungs, but without markerd sequestration of parasitized red blood cells in the pulmonary microvasculature were histopathologically observed in a single fatal case of vivax malaria[17].

Drug induced reversible small airway obstruction was observed in 34 patients as assessed by the spirometry. In patients with pulmonary symptoms, a marked decrease in PEFR and slowed recovery (9.6 days) was observed[10].

Over the last one decade there has been a significant change in the clinical manifestations of malaria from this region[18]. Our study revealed that anemia was present in 33.5% and jaundice in 29% cases. This could be attributed to changes in the environment due to various causes. Possibility of changes in the antigenic and pathogenic characteristics of the parasite cannot be ruled out. There remain the possibilities of assimilation of the genes responsible for various antigenic attributes by the parasite from different regions of the country like Bihar, Tripura and Gujarat.

The awareness about the changing spectrum of severe malaria is of great importance to every level of health care provider. Our results suggest that pulmonary involvement is seen in a significant number of patients mostly 20–40 yr age group working outside who are most susceptible, with almost 10% infected with *P. vivax*. If these clinical presentations are ignored, it may lead to delay in diagnosis and can alter the outcome and prognosis of the disease. Therefore, early diagnosis of malaria induced ARDS can significantly affect the outcome and may reduce the mortality rate associated with this complication.

REFERENCES

1. Greenwood BM, Fidock DA, Kyle DE, Kappe SH, Alonso PL, Collins FH, Duffy PE. Malaria: progress, perils, and prospects for eradication. *J Clin Invest* 2008; *118:* 1266–76.
2. Malaria disease burden in SEA region. New Delhi: World Health Organization (South-East Asia Regional Office). Available from: *http://www.searo.who.int/EN/Section10/Section21/Section340_4018.htm.*
3. Jindal SK, Aggarwal AN, Gupta D. Adult respiratory distress syndrome in the tropics. *Clin Chest Med* 2002; *23:* 445–55.
4. Sarkar S, Saha K, Das CS. Three cases of ARDS: an emerging complication of *Plasmodium vivax* malaria. *Lung India* 2010; *27*(3): 154–7.
5. Anstey NM, Jacups SP, Cain T, Pearson T, Ziesing PJ, Fisher DA, Currie BJ, Marks PJ, Maguire GP. Pulmonary manifestations of uncomplicated falciparum and vivax malaria: cough, small airway obstruction, impaired gas transfer, and increased pulmonary phagocytic activity. *J Infect Dis* 2002; *185*(9): 1326–34.
6. Maguire GP, Handojo T, Pain MC, Kenangalem E, Price RN, Tjitra E, Anstey NM. Lung injury in uncomplicated and severe falciparum malaria: a longitudinal study in papua, Indonesia. *J Infect Dis* 2005; *192*(11): 1966–74.
7. Kumar A, Valecha N, Jain T, Dash AP. Burden of malaria in India: retrospective and prospective view. *Am J Trop Med Hyg* 2007; *77:* 69–78.
8. Taylor WR, Canon V, White NJ. Pulmonary manifestations of

malaria: recognition and management. *Treat Respir Med* 2006; *5:* 419–28.
9. Agarwal R, Nath A, Gupta D. Noninvasive ventilation in *Plasmodium vivax* related ALI/ARDS. *Intern Med* 2007; *46*(24): 2007–11.
10. Price L, Planche T, Rayner C, Krishna S. Acute respiratory distress syndrome in *Plasmodium vivax* malaria: case report and review of the literature. *Trans R Soc Trop Med Hyg* 2007; *101*(7): 615–9.
11. Gozal D. The incidence of pulmonary manifestations during *Plasmodium falciparum* malaria in non immune subjects. *Trop Med Parasitol* 1992; *43*(1): 6–8.
12. Mishra U, Ray G. Pulmonary manifestation of malaria. American College of Chest Physician 2005. Available from: *http://meeting.chestpubs.org/cgi/content/abstract/128/4/376S-a*
13. Rajput R, Singh H, Singh S, Meena Tiwari UC. Pulmonary manifestation in malaria. *J Indian Med Assoc* 2000; *98*(10): 612–4.
14. Tong MJ, Ballantine TV, Youel DR. Pulmonary function studies in *Plasmodium falciparum* malaria. *Am Rev Respir Dis* 1972; *106:* 23–9.
15. Applebaum IL, Shrager J. Pneumonitis associated with malaria. *Arch Int Med* 1944; *74:* 155–62.
16. Mohan A, Sharma SK, Bollineni S. Acute lung injury and acute respiratory distress syndrome in malaria. *J Vector Borne Dis* 2008; *45*(3): 179–93.
17. Valecha N, Pinto RG, Turner GD, Kumar A, Rodrigues S, Dubhashi NG, Rodrigues E, Banaulikar SS, Singh R, Dash AP, Baird JK. Histopathology of fatal respiratory distress caused by *Plasmodium vivax* malaria. *Am J Trop Med Hyg* 2009; *81*(5): 758–62.
18. Kochar DK, Kumawat BL, Bajiya HN, Chauhan S, Kochar SK, Agarwal RP. Profhylactic role of single dose phenobarbitone is preventing convulsion in cerebral malaria. *J Assoc Phys India* 1997; *45*(2): 123–4.

Correspondence to: Dr Surendra Kumar, Associate Professor, H–2, PBM Hospital Campus, Bikaner–334 003, India.
E-mail: drsurendrakumar@rediffmail.com

Received: 11 June 2011 *Accepted in revised form:* 26 September 2011