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Original Research Article

Acute respiratory distress syndrome in Vivax malaria in children

Amitesh Yadav[1], Yashwant Kumar Rao[1]*, Tanu Midha[2], Sunisha Arora[1]

[1]Department of Pediatrics, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India
[2]Department of Community Medicine, Government College Kaanauj, Uttar Pradesh, India

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***Correspondence:**
Dr. Yashwant Kumar Rao,
E-mail: ykraoneo@yahoo.co.in

ABSTRACT

Background: Malaria, the most important protozoal disease in humans remains the significant health problem globally. The objective of this study was to study the acute respiratory distress syndrome in children in vivax malaria.
Methods: This prospective study enrolled children with acute febrile illness aged 1-15 years who diagnosed as malaria. Then we searched the children who present with acute (<7 days) history of respiratory distress and fulfill the ARDS criteria.
Results: Among 112 children, enrolled in the study 70 (62.5%) were vivax malaria and 42 (37.5%) were falciparum malaria.21 children were diagnosed as ARDS (The level of PaO2/FiO2 was <200). 42.9% children had ARDS due to vivax and 57.1% due to falciparum. The p-value of 0.039 was obtained denoting a significant association. It was noted that the percentage of vivax and falciparum causing ARDS was comparable. Thus, it showed there is a rising propensity of vivax to cause respiratory failure.
Conclusions: ARDS is an important severe complication of malaria. Previously it was noted mainly with falciparum but now days there is rising propensity of vivax to cause respiratory failure. ARDS in malaria has high mortality so early diagnosis and appropriate treatment with antimalarial drugs can be lifesaving.

Keywords: Acute respiratory distress, Acute lung injury, Falciparum, Malaria, Vivax

INTRODUCTION

Malaria, the most important protozoal disease in humans remains the significant health problem globally. Malaria is endemic in the tropics and subtropics with India as a major contributor to the morbidity and mortality in the South-East Asian region.[1] Children form a great part of the Indian population; the percentage of malarial deaths is very high. India contributes to 77% of the total malaria in South East Asia and about 95% of the population of moderate to high risk of malaria in SEA region is living in India.[2] The WHO African region carries a disproportionately high share of the global malaria burden. In 2015, the region was home to 90% of malaria cases and 92% of malaria deaths. Malaria is caused by obligate intraerythrocytic protozoa of the genus *Plasmodium*. Humans can be infected with one (or more) of the following four species: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Plasmodia are primarily transmitted by the bite of an infected female Anopheles mosquito, but infections can also occur through exposure to infected blood products (transfusion malaria), by congenital transmission, sharing of contaminated needles and organ transplantation.[3] *P. falciparum* is the main cause of malaria and death, but *P. vivax* is also now emerging to cause severe malaria in many cases. After *P. falciparum*, *P. vivax* is the next most significant malaria species; both often coexist in several parts of world. However, the prevalence of these two species is approximately equal in the Indian subcontinent.[4] In children uncomplicated malaria usually present with fever and non-specific symptoms, complicated malaria

present with severe anemia, spontaneous bleeding, convulsions, multi-organ involvement, respiratory distress (ARDS, ALI). In recent years incidence of complicated malaria has increased. Severe life-threatening malaria is mainly due to p. falciparum recently ARDS and ALI cases are also seen with vivax malaria mainly in young population.[5]

In this study we describe the epidemiology, clinical and laboratory presentations of *P. vivax* and *P. falciparum* in children admitted to the Pediatrics Department of GSVM Medical College, Kanpur. The results for both the species were compared and a special emphasis was given to children having acute respiratory distress.

METHODS

This prospective study was carried out at the Department of Pediatrics, GSVM Medical College, Kanpur, UP, India from April 2016 to march 2017.

Inclusion criteria

Any child with age 1-15 years who present with acute febrile illness was admitted in the hospital and if diagnosed as malaria after RDT and microscopy was included in the

Malaria diagnosis

Diagnosis, species and number of parasites were determined by Giemsa stained thick and thin peripheral blood films and examined under oil emersion. The slide was considered negative when there were no parasites in the 100-high-power field. The PBF was reviewed 2 times by experienced microscopists. The RDTs were based on detection of specific Plasmodium antigen, Lactate dehydrogenase (OptiMal test; Diamed AG, Cressier sur Morat, Switzerland) and histidine-rich protein-2 (Falcivax test; Zephyr Biomedical System, Goa, India).

Clinical evaluation

After the diagnosis, clinical evaluation was done. The patient demographics and clinical details were recorded in a standard proforma. This included age, sex, religion, symptoms and signs of the patient. Other standard evaluation included body weight, assessment of blood pressure, heart and respiratory rates, axillary temperature, systems examination and description of the general condition of the patient.

Laboratory procedures

The following laboratory procedures were done for all the patients involved in the study. Complete blood count, platelet count, hemoglobin, serum electrolytes, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALP), ABG (PaO2/FiO2 ratio) and serum creatinine.

ARDS criteria[6]

Any child who fulfill the following criteria was diagnosed as ARDS.

- Acute onset (<7 days)
- Severe hypoxemia (Pao2/Fio2 < 300 for acute lung injury, or <200 for acute respiratory distress syndrome)
- Diffuse bilateral pulmonary infiltrates on frontal radiograph consistent with pulmonary edema (these can be patchy and asymmetric, and pleural effusions can be present).
- Absence of left atrial hypertension (pulmonary artery wedge pressure <18 mm Hg if measured).

RESULTS

During the study period the total number of children included in the study was 112. They were selected from the Department of Pediatrics, GSVM Medical College, and Kanpur. They were diagnosed positive for malaria parasite by blood films, thick and thin smears. 62.5% (70) of the patients were positive for *P. vivax* and 37.5% (42) were positive for *P. falciparum*. The data obtained was tabulated and compared. These are presented in the Tables 1, 2, 3 and 4.

Table 1 shows the patient characteristics which includes the age, sex and religion. All of them were positive for falciparum. In 1-5 years of age group, out of 31 patients, 16 (51.6%) had vivax and 15 (48.4%) had falciparum malaria. A total of 68 patients belonged to age group of 5-15 years. Of these 54 (69.2%) had vivax and 24 (30.8%) had falciparum malaria. The number of males in the study were 64 with 43 (67.2%) having vivax and 21 (32.8%) having falciparum malaria. There were 48 females and 27 (56.2%) had vivax whereas 21 (43.8%) had falciparum malaria. The result of gender distribution was not found to be significant (p=0.237). Though vivax was found in more number of cases than falciparum in both Hindus and Muslims, it did not bear any significance (p=0.690).

Table 1: Characteristics of *P. vivax* and *P. falciparum* cases

Characteristic	P. vivax (n=70)		P. falciparum (n=42)		p-value
Age (years)	**No.**	**%**	**No.**	**%**	
0-1	0	0	3	100	0.018
1-5	16	51.6	15	48.4	
5-15	54	69.2	24	30.8	
Sex					
Male	43	67.2	21	32.8	0.237
Female	27	56.2	21	43.8	
Religion					
Hindu	58	61.7	36	38.3	0.690
Muslim	12	66.7	6	33.3	

Table 2 shows the clinical presentation of the patients infected with *P. vivax* and *P. falciparum*.

Table 2: Symptoms of *P. vivax* and *P. falciparum* cases.

Symptoms	P. vivax (n=70)		P. falciparum (n=42)	
	No.	%	No.	%
Intermittent fever	33	47.1	15	35.7
Respiratory Distress	12	17.1	15	35.7
Abdominal symptoms	39	55.7	21	50
CNS symptoms	19	27.1	9	21.4
Pallor	60	85.7	36	85.7
Icterus	9	12.9	6	14.3
Edema	15	21.4	12	28.6
Hypotension	3	4.3	0	0
Hepatomegaly	49	70	33	78.6
Splenomegaly	51	72.9	30	71.4

Out of 70 children infected with *P. vivax*, intermittent fever was present in 33 (47.1%), respiratory symptoms in 12 (17.1%), abdominal symptoms in 39 (55.7%), CNS symptoms in 19 (27.1%), pallor in 60 (85.7%), icterus in 9 (12.9%), edema in 15 (21.4%), hypotension in 3 (4.3%), hepatomegaly in 49 (70%) and splenomegaly in 51 (72.9%). For *P. falciparum*, the same symptoms had different percentages as follows: intermittent fever was present in 15 (35.7%), respiratory symptoms in 15 (35.7%), abdominal symptoms in 21 (50%), CNS symptoms in 9 (21.4%), pallor in 36 (85.7%), icterus in 6 (14.3%), edema in 12 (28.6%), hepatomegaly in 33 (78.6%) and splenomegaly in 30 (71.4%). Hypotension was not found in any patient of *P. falciparum*.

The features which were present in more percentage of the cases infected with *P. vivax* were intermittent fever, abdominal symptoms, CNS symptoms, hypotension and splenomegaly. However, in *P. falciparum* the symptoms like respiratory, icterus, edema and hepatomegaly were more commonly reported. Among these, pallor, icterus and splenomegaly were more or less found in equal number of the patients.

In Table 3 and Table 4, laboratory findings of both vivax and falciparum malaria cases are reported. Out of the total cases in which electrolyte imbalance was present (58, 51.8%), greater percentage belonged to vivax cases (58.6%) than falciparum cases (41.4%).

The patients who had hepatic dysfunction showed a rise in the markers like SGOT [49 cases (vivax = 57.1%, falciparum = 43.9%)], SGPT [64 cases (vivax = 67.2%, falciparum = 32.8%)] and serum ALP [54 cases (vivax = 66.7%, falciparum = 33.3 %)]. A significant association ($p<0.05$) was found in the levels of serum creatinine, TLC and platelet count.

Table 3: Laboratory findings of *P. vivax* and *P. falciparum* cases.

Characteristic	P. vivax (n=70)		P. falciparum (n=42)		p-value
Electrolyte imbalance	**No.**	**%**	**No.**	**%**	
Present	34	58.6	24	41.4	0.379
Absent	36	66.7	18	33.3	
SGPT					
Raised	43	67.2	21	32.8	0.237
Normal	27	56.2	21	43.8	
SGOT					
Raised	28	57.1	21	43.9	0.302
Normal	42	66.7	21	33.3	
Serum creatinine					
Raised	9	42.9	12	57.1	0.039
Normal	61	67	30	33	
PaO2/FiO2					
<200	9	42.9	12	57.1	0.039
Normal	61	67	30	33	

Table 4: Laboratory findings of *P. vivax* and *P. falciparum* cases.

Characteristic	*P. vivax* (n=70)		*P. falciparum* (n=42)		p-value
	Mean	SD	Mean	SD	
Duration of fever (days)	7.9	5.7	8.5	5.4	0.696
Hb (g/dl)	5.9	2.0	5.9	2.1	0.956
TLC	7194	396	1002	623	0.006
Neutrophil %	59.9	9.1	57.2	14.4	0.284
Lymphocyte%	45.5	10.4	46.8	11.5	0.521
Eosinophil %	2.6	1.5	2.8	1.6	0.158
Monocyte %	4.8	2.0	4.2	1.9	0.622
Platelet count	84400	8708	146000	15913	0.024

The level of PaO2/FiO2 was <200 in 21 patients of whom 42.9% of the patients had vivax and 57.1% had falciparum. The p-value of 0.039 was obtained denoting a significant association. These patients had ARDS. It was

noted that the percentage of vivax and falciparum causing ARDS was comparable. Thus, it showed there is a rising propensity of vivax to cause respiratory failure.

DISCUSSION

Plasmodium falciparum may have been considered the cause for severe malaria up till now, but recent studies from India, Indonesia, Papua New Guinea, and Pakistanhave shown that *Plasmodium vivax* is also emerging as a cause for cases of severe malaria. Also, there is evidence of increasing incidence of acute respiratory distress in *P. vivax* cases.[7-10]

With this background, this study was designed to describe the epidemiology, clinical and laboratory presentations of *P. vivax* and *P. falciparum* in children admitted to the Pediatrics Department of GSVM Medical College, Kanpur. The results for both the species were compared and a special emphasis was given to children having Acute respiratory distress.

The maximum malaria cases belonged to the age group of 5-15 years with higher proportion of vivax cases. Whereas the ratio of males to females was approximately equal in patients with *P. falciparum*, there was a consistent predominance of males in patients with *P. vivax* malaria. Since the symptoms of uncomplicated vivax and falciparum malaria are similar treatment seeking or referral biases are unlikely.

The clinical symptoms of malaria are primarily due to schizont rupture and destruction of erythrocytes. Malaria can have a gradual or a fulminant course with nonspecific symptoms. The presentation of malaria often resembles those of common viral infections; this may lead to a delay in diagnosis. The majority of patients experience fever (>92% of cases), chills (79%), headaches (70%), and diaphoresis (64%). Other common symptoms include dizziness, malaise, myalgia, abdominal pain, nausea, vomiting, mild diarrhea, and dry cough. Physical signs include fever, jaundice, pallor, orthostatic hypotension, hepatomegaly, and splenomegaly.

Thrombocytopenia is the most common laboratory abnormality (60% of cases), followed by hyperbilirubinemia (40%), anemia (30%), and elevated hepatic aminotransferase levels (25%). The leukocyte count is usually normal or low, but neutrophilia with a marked increase in band forms (left shift) is present in the majority of cases.

The major complications of severe malaria include cerebral malaria, ARDS, acute renal failure, severe anemia, and/or bleeding. Acidosis and hypoglycemia are the most common metabolic complications. Any of these complications can develop rapidly and progress to death within hours or days. The results of the present study showed that there is increase in cases of severe malaria infected with *P. vivax*.

Severe anemia is common in children in highly endemic areas due to chronic or repeated infections. In the present study 85.7% of patients had pallor with mean hemoglobin of 5.9 g/dl. This was for both vivax and falciparum. The findings were consistent with the study from Bikaner, Indonesia and Gabon.[11] It is not associated with high case fatality rate.

Thrombocytopenia as defined by platelet counts under 150,000/μL seems to be very frequent among patients with vivax malaria and apparently more frequent in vivax than in falciparum patients despite not being a consensus. The present study found the mean platelet count as 84,400/μL in *P. vivax* cases and 146,000/μL in *P. falciparum* cases. This shows that thrombocytopenia is also common in *P. vivax* cases.

Intermittent fever was present in 47.1% of *P. vivax* cases and 35.7% of *P. falciparum* cases. It has been established that the classical malaria paroxysms are of eight hours with fever almost invariably present. Other accompanying symptoms may include chills, rigors, sweating, headache, nausea, vomiting and body aches. Fever occurs even with lower parasitaemia (100 infected RBCs/microliter). Thus, in the present study, greater percentage of patients with *P. vivax* showed intermittent fever. However, the overall percentage of patients with febrile syndrome was lesser as normally expected (less than 50% for both species). Self-medication with antipyretic or antimalarial agents may contribute to this finding. Sometimes, even non-immune persons are afebrile on admission.

Cerebral malaria is the most lethal entity of severe malaria and children are more prone than other susceptible groups. Although *P. falciparum* is the usual pathogen, recently *P. vivax* is also reported as an emerging pathogen to cause this severe disease in children. There were 27.1% children of with CNS symptoms caused by *P. vivax* and 21.4% by *P. falciparum* in this study. In a study from India cerebral malaria was present in 21.5% and 13.9% children having *P. falciparum* and *P. vivax* infections, respectively.[12]

Hepatic dysfunction was characterized by icterus (13%), hepatomegaly (73.2%), splenomegaly (72/3%) and elevated liver enzymes SGPT (57%), SGOT (43.75%) and AST (48.2%). The signs of hepatic dysfunction mentioned, were present more commonly in cases of *P. falciparum* but the elevated enzymes were found more in cases of *P. vivax*. In the present study it is seen that patients with vivax maybe equally suffer from hepatic dysfunction. Other studies from India showed that lesser percentage vivax patients had signs of hepatic dysfunction which is similar to present study.[13] However, the present study also shows that vivax can cause elevation in liver enzymes more than falciparum which is contrast with other studies. Some studies have shown that there is an increase in liver enzymes in vivax cases but not more than falciparum cases.[14] The elevated enzymes

suggest that there is hepatocellular injury associated with malaria.

Acute renal failure is suspected in cases of oliguria and confirmed if serum creatinine is higher than 3.0 mg/dL. It has been shown to be associated mainly with falciparum, but there have been recent evidences suggesting that vivax can also be complicated by acute renal failure. The Bikaner study reported 30.4% cases of falciparum and 15.4% cases of vivax having ARF.[15] These results were comparable to the present study which showed 28.5% cases of falciparum and 12.8% cases of vivax having ARF. Thus, there is evidence that *P. vivax* is emerging as a cause for ARF in children. The prognosis of isolated ARF not associated with any other organ dysfunction is good.

Respiratory distress is a complication more often associated with *P. falciparum* than with *P. vivax*. In the present study 42.9% children with vivax malaria were diagnosed as ARDS while 57.1% children with falciparum malaria had ARDS. The p-value of 0.039 was obtained denoting a significant association. It was noted that the percentage of vivax and falciparum causing ARDS was comparable. Thus, it showed there is a rising propensity of vivax to cause respiratory failure.

Two studies from India and one from Africa also shows similar findings, where cases of vivax showing respiratory distress were less than 10%.[16-18] A study among Gabonese children showed that 31% of falciparum affected children had respiratory distress.[19] Results from many studies consistently show that respiratory distress is a life-threatening syndrome in childhood malaria. The etiology described is acute respiratory distress/ noncardiogenic pulmonary edema. Earlier it was thought to occur in falciparum alone but now it is described even in vivax cases.[19,12]

CONCLUSION

The present study provides significant evidence that *P. vivax*, which was once considered to be a benign parasite, is causing morbidity almost similar to *P. falciparum*. It is emerging as a cause of severe and complicated malaria. It is frequently associated with multi organ dysfunction which increases the mortality. Acute respiratory distress syndrome is a significant life threating complication of *P. vivax* now. Early diagnosis and appropriate treatment of ARDS can save the life. As efforts are being made to eradicate malaria globally, special emphasis should be given to burden by P. vivax. More studies should be focused on underlying pathogenesis so that adequate measures can be taken to prevent any permanent damage.

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