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Emerging new trends of malaria in children: A study from a tertiary care centre in northern India

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ABSTRACT

Background & objectives: Vivax malaria has long been considered a benign entity. However, an increasing number of reports are highlighting that it may no longer be so. An investigation was carried out to study the profile of malarial admissions in a tertiary care pediatric hospital and to analyse the burden of vivax-related complications.

Methods: It is a retrospective observational study. The medical case records of all the patients admitted in the year 2011 with the clinical diagnosis of malaria and laboratory evidence in the form of positive peripheral smear and/or rapid malarial antigen test were retrieved and retrospectively analysed.

Results: Overall, 198 cases were included, 128 (64.6%) were due to *Plasmodium vivax*, 66 (33.3%) due to *P. falciparum* and 4 (2%) had evidence of mixed infection of *Pv* + *Pf*. The clinical features on admission were similar in all the groups. In total, 64/128 (50%) patients with vivax infection had one or more complications with severe anemia in 33 (26%) and cerebral malaria in 16 (12.5%). Six deaths were reported in *P. vivax* cases. In the falciparum group, 52 (78.8%) had one or more complications with severe anemia in 37 (56.1%) and cerebral malaria in 24 (36.4%). Four deaths were reported in *P. falciparum* cases.

Interpretation & conclusion: Overall because of their larger numbers, vivax patients outnumbered other groups, with regards to severe complications and deaths. It was concluded that vivax malaria is emerging as an important cause of malaria-related complications in children.

Key words Cerebral malaria; children; *Plasmodium falciparum; P. vivax*

INTRODUCTION

India is the major contributor to malaria burden in Southeast Asia[1]. In a recent study by "million death collaboration", it was estimated that malaria accounts for 205,000 deaths per year in India, with 55,000 deaths occurring in early childhood[2]. These numbers though have been questioned by some[3] as they do highlight that the problem is much more than previously presumed.

Malaria due to *P. falciparum* has been historically associated with severe complications and mortality. However, *P. vivax* is now increasingly being reported as a cause of severe malaria from countries across the globe. Unusual manifestations like glomerulonephritis and gastroenteritis have also been reported[4–5].

This study was planned with the objectives to study the profile of malarial admissions in a tertiary care pediatric (<12 yr age) hospital of northern India and to assess the contribution of *P. vivax* infection to the morbidity and mortality.

MATERIAL & METHODS

This retrospective study was conducted at a pediatric tertiary care hospital located at New Delhi, India. This is a referral centre for children up to 12-yr of age and receives patients from Delhi and its surrounding states. The data pertaining to inpatient cases of malaria were collected for the entire year 2011. For enlisting of cases, central registration numbers were obtained from the medical records department (using ICD-10 codes) and from the laboratory (cases with peripheral smear positive for malaria and/or positive rapid malaria antigen test). A final list of cases was compiled from two sources and the electronic scanned case records were retrieved and reviewed. Detailed clinical, biochemical and hematological characteristics along with the course of hospital stay of each case record was entered in a pre-designed proforma and transferred to a Microsoft Excel sheet. The laboratory data mentioned in the case records were cross-checked directly with the laboratory records for each patient. The rapid malaria antigen kit used at the study centre was based on detection of lactate dehydrogenase and histidine-rich protein-2.

In the final analysis, only cases with clinical picture consistent with malaria along with presence of malarial parasite on peripheral smear and/or positive rapid malarial antigen test (from the hospital laboratory or outside

laboratory, in case, the patient was referred with an established diagnosis) were included. Thus, those with clinical diagnosis of malaria but without any evidence on smear or antigen testing were not included.

Based on the results of peripheral smear and/or rapid malaria test, the cases were categorized into three groups: vivax malaria, falciparum malaria and mixed (*Pv +Pf*) malaria. Complications such as cerebral malaria, acute renal failure (ARF), shock, severe anaemia and hypoglycemia were defined as per WHO guidelines[6]. Hepatitis was defined as patients having clinical jaundice and conjugated hyperbilirubinemia with or without raised enzyme levels and negative viral studies. Severe thrombocytopenia was defined as platelet count <20,000/mm^3 and disseminated intravascular coagulation (DIC) was defined as patients with clinical features of bleeding with presence of coagulopathy (prolonged prothrombin time and activated partial thromboplastin time) and thrombocytopenia.

In addition, patients with raised urea (>50 mg%) and creatinine levels (<3 mg/dl), which subsequently improved without any specific intervention, were defined as having prerenal azotemia. Hyponatremia and hypernatremia were defined as serum sodium <130 meq/l and >150 meq/l, respectively. Hypokalemia was defined as serum potassium <3.5 meq/l and hyperkalemia as >5.5 meq/l. The complications that could be attributed to non-malarial etiologies were excluded from the data.

Other investigations were carried out to rule out co-existing conditions, depending on the clinical situation. Patients received treatment for malaria as per WHO guidelines[6]. Supportive treatment was given as per the departmental protocols. The study protocol was approved by the institutional scientific committee. The data were analyzed using Epi Info version 3.1. The median and interquartile ranges were reported for continuous variables. Proportions were reported for categorical variables and to detect statistically significant difference between the groups, Kruskal-Wallis test was used for continuous variables (medians) and chi-square test for categorical variables (proportions).

RESULTS

A total of 211 case records of the year 2011 with clinical/laboratory diagnosis of malaria were retrieved. In 13 cases, clinical diagnosis of malaria was made but those lacked laboratory evidence, therefore, the remaining 198 cases were analyzed. The median age was 48 months with range of 1–144 months, 117 (59.1%) children were in the age range of 0–5 yr and 119 (60.1%) were males. A total of 114 (57.6%) patients were residents of Delhi, whereas 82 (41.4%) were from the neighbouring state of Uttar Pradesh. Most of the cases (93.5%) were admitted during the months of June and October. Peripheral smears were available in 173 (87.4%) patients and were positive in 140 (70.7%) patients. The rapid malaria antigen test was done in 183 (92.4%) patients and found positive in 173 (87.4%) patients where 128 (64.6%) patients had vivax malaria, 66 (34.3%) had falciparum malaria and 4 (2%) had mixed infection.

The median age at presentation was significantly lower in vivax group (42 months) as compared to falciparum group (60 months). Also the proportion of males was more in the vivax group (64%) than falciparum group (50%). Fever was present in all the cases except for one neonate with vivax infection. With regard to the frequency of most of the clinical manifestations, there was no statistically significant difference among three groups except for altered sensorium which was more common in falciparum group.

The complications seen in the three groups are summarized in Table 1. Overall, 118 (59.6%) patients had severe complication, out of which 76 (64.4%) were in the age range of 0–5 yr. The proportion of cases with severe complications was significantly more in the falciparum group (78.8% as compared to 50% each in vivax and mixed group). However, the actual number of patients with severe complications in vivax group was more than the combined numbers in other two groups (Table 1). Severe anaemia, cerebral malaria, and acute respiratory distress syndrome (ARDS) were significantly more common in the *P. falciparum* group.

In one patient with altered sensorium and evidence of hepatitis, hepatitis B surface antigen was found positive, with raised hepatitis B antigen levels. As these manifestations could be due to hepatitis B, the same were not taken as complications of malaria. Apart from cases with cerebral malaria, eight patients had seizures, which were considered to be febrile seizures. Lumbar puncture reports were available in 18 patients with cerebral malaria. Four showed lymphocytic pleocytosis and in five cases proteins were elevated. Eight cases were diagnosed as acute renal failure and received hemodialysis or peritoneal dialysis. Seven out of these eight were from vivax group. Ten patients died and in 18 cases outcome was not known. Eight out of 10 deaths occurred in children of 0–5 yr age group. Mortality rate was more in the falciparum group, though the absolute numbers of deaths were more in the vivax group. All the patients who died had multiple severe complications. Cerebral malaria was present in 8 out of 10 patients who died.

Table 1. Complications and mortality among three groups

Severe complication	No. of vivax group (n=128)	No. of falciparum group (n=66)	Mixed group (n=4)	*p*-value
Cerebral malaria	16 (12.5)	24 (36.4)	1 (25)	<0.001
Severe anaemia	33 (25.8)	37 (56.1)	1 (25)	<0.001
Severe thrombocytopenia	13 (10.2)	9 (13.6)	0 (0)	0.59
Hepatitis	14 (11.1)	12 (16.7)	1 (25)	0.43
DIC	3 (2.3)	2 (3)	0 (0)	0.90
Acute renal failure	7 (5.5)	1 (1.5)	0 (0)	0.38
Hypoglycemia	0 (0)	1 (1.5)	0 (0)	0.36
ARDS	1 (0.8)	5 (7.6)	0 (0)	0.03
Shock	10 (7.8)	8 (12.1)	0 (0)	0.50
Respiratory failure	7 (5.5)	9 (13.6)	0 (0)	0.11
MODS	4 (3.1)	2 (3)	0 (0)	0.93
Cases with one or more complication	64 (50)	52 (78.8)	2 (50)	<0.001
Other complications				
Prerenal azotemia	29 (22.7)	30 (45.5)	0 (0)	0.001
Hyperglycemia	0 (0)	2 (2.9)	0 (0)	0.13
Hypokalemia	4 (3.1)	3 (4.5)	0 (0)	0.81
Hyponatremia	3 (2.3)	2 (3.0)	0 (0)	0.90
Coagulopathy	6 (4.7)	6 (9.1)	1 (25)	0.29
Mortality	6 (4.7)	4 (6.1)	0 (0)	0.82

Figures in parenthenses indicate percentages.

DISCUSSION

The present study showed that *P. vivax* is a significant cause of morbidity and mortality in pediatric age group. Although the complication rate is more in falciparum infection, vivax is responsible for more than half of the severe malaria cases. The spectrum of complications seen in vivax infection is same as of falciparum infection.

Since, time immemorial *P. vivax* has been considered a benign entity and hence the term 'benign tertian malaria' has been used to describe it. However, recent studies are challenging this term[7–11]. Studies from northern India and Pakistan showed that 40–64% malarial admissions are accounted by vivax malaria with severe disease in 30–63% of these patients, which is consistent with the results of the present study[7–11]. Studies done in other countries have also shown that *P. vivax* can cause severe malaria, though the proportion of cases with *P. vivax* infection was much less[12–14].

The basic mechanism underlying the complications in both the vivax and falciparum malaria is similar but the degree of contribution by the individual multiple factors differs. Complications such as cerebral malaria, renal failure, hepatic involvement and ARDS are believed to be due to sequestration of infected red cells in microvasculature. Other complications such as severe anaemia, disseminated intravascular coagulation and thrombocytopenia are considered to be non-sequestration related with a multifactorial etiology, e.g. hemolysis of infected and uninfected red cells, reduced red cell deformability, decreased platelet survival and increased uptake[15–18].

Involvement of central nervous system in benign tertian malaria is known to occur since year 1921[19]. There have been incidental reports since then with the last decade seeing an ever increasing number. In the present study, 16 (12.5%) cases with *P. vivax* monoinfection had cerebral malaria. In the studies from Bikaner and New Delhi, cerebral malaria was reported in 21.5 and 16.8% of children with severe vivax malaria, respectively[8–9].

Anaemia has been widely observed in both vivax and falciparum malaria. In our study, severe anaemia was significantly more common in the falciparum group than the vivax group. This has been observed in other studies also. This may be because the vivax cases generally have lower parasite densities and, therefore, the likelihood of having profound anaemia is less[18].

Renal manifestations of malaria can range from prerenal azotemia to acute renal failure, nephrotic syndrome and acute glomerulonephritis[20–22]. In a study from Karachi, Pakistan, 36 of 75 children with acute malaria had prerenal azotemia, 30% of which were owing to *P. vivax*. No case had ARF[10]. In the present study, prerenal azotemia was present in almost half of the *P. falciparum* group and about one-fourth of the vivax group. Interestingly, in the present study, seven cases of vivax group and only one of falciparum group had renal failure requiring dialysis.

In the present study, severe thrombocytopenia and DIC was present in both the vivax and falciparum groups in almost equal proportions. Although, profound thrombocytopenia is considered uncommon in vivax malaria, recent articles are reporting this with increasing frequency[7–9, 12]. Further, six out of 10 malarial deaths were due to *P. vivax*, which is indeed an important finding. In the pediatric study from Bikaner, deaths occurred in 4/65 children of the vivax group, as compared to 6/79 of falciparum group[7]. Deaths due to vivax malaria have been reported in significant numbers in other studies also[9].

This study had certain limitations, such as species confirmation was not made by further tests like polymerase chain reaction (PCR) and parasite density was also not estimated. Species-specific PCR increases the diagnostic accuracy and can detect submicroscopic infections. However, it was not available in our research. This study also represents only those cases of malaria that were admitted into the hospital. Thus, the complication rates cannot be generalized to the population at large. The major strengths of this study were the strict defining criteria for cerebral malaria, renal failure and other severe complications. Our data also have probably the largest number of cases in a single year.

To conclude that *P. vivax* is emerging as an important cause of malarial morbidity and mortality. There is a need to strengthen our strategies to combat this growing menace.

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