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Longitudinal cohort study of epidemiology of *P. falciparum* malaria infection in children & different spectrum of complications in an area of intense malaria transmission

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Abstract

Objective: Longitudinal cohort study of epidemiology of p. falciparum malaria infection in children & different spectrum of complication in area of intense malaria transmission. **Materials & Methods:** The study was carried out between Oct 2005 and Sept 2006 in the Department of Paediatrics PMCH Patna. All children (up to 18 yrs of age with fever of short duration visited to hospital either in OPD or indoor without any documented pre-existing systemic illness were included in this study. The cases for present study were selected on random basis amongst the case of malaria as per following protocol. Primary pool patients of all age groups, religion, presented with fever of short duration without any documented pre-existing illness and tested for malaria parasite via PBS (thick & thin smear) and rapid antigen test. Secondary pool cases from primary pool with definite diagnosis of p. falciparum malaria, were further divided into uncomplicated & complicated group according to WHO criteria 2000. **Results:** The study included 18,700 febrile children who were presented in OPD & indoor in PMCH from Oct 2005 and Sept 2006. All cases selected in the study were diagnosed by microscopy and rapid diagnostic test. Incidence of p. falciparum malaria among febrile children was 84%. Incidence of p. falciparum was 16% of total malaria cases. Incidence of p. falciparum in febrile male children 60% was more than female febrile children 40%. Incidence of p. falciparum in Hindu febrile children (80%) was more than muslim children. Among the p. falciparum positive cases complicated cases were 43.5% and uncomplicated cases were 56.67%. The commonest age group of p. falciparum was in between 5-10 yrs (40%), followed by in <5 yrs (29%), in 10-15 yrs (25.33%) and >15 yrs (5.67%). Cerebral anemia was commonest complication (29.23%) of p. falciparum infection followed by jaundice (29.2%), hypoglycaemia (29.2%), and severe anemia (24.6%). MODS (21.33%), ARDS (3.07%), shock (3.07%), DIC (1.5%), acidosis (4.61%), ARF (6.15%) were uncommon complications. **Conclusion:** During this study, it was observed that p. falciparum malaria account for good number cases among febrile children. It should be screened for in any child present with fever along with hepatomegaly and or spleenomegaly to diagnose early. Once diagnose p. Falciparum, should be treated & managed urgently and appropriately to prevent dreaded complications, and so that mortality and morbidity due to complicated malaria could prevented or decreased.

Keywords: P.falciparum, MODS-Multi organ dysfunction syndrome, ARDS-Acute respiratory distress syndrome, ARF-Acute renal failure, DIC-Disseminated intravascular coagulation.

Introduction

WHO has identified six infectious diseases as the world's biggest killer of children & young adult and called for renewed global effort to contain them. The six diseases are- AIDS, malaria, TB, measles, ARI account for 90% of the all deaths.

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Malaria is a parasitic disease caused by protozoan microorganism of genus plasmodium. They are more than 120 species of plasmodium but only four of them –p.vivax, p.faciparum, p.ovale and p.malariae have capability of causing human malaria. It is transmited to man by female anopheles mosquito[1].The incidence of malaria worldwide is estimated to be 300-500 million clinical cases each year, with about 90%, this occurring sub Saharan Africa & mostly caused by p.falciparum. It is thought to kill between 1.1 to 2.7 million people worldwide each year, of whom above 1 million are children under the age of 5 yrs in these area[2].In 2017, there were an estimated 219 million cases of malaria in 87 countries. The estimated number of malaria deaths

stood at 435 000 in 2017. The WHO African Region carries a disproportionately high share of the global malaria burden. In 2017, the region was home to 92% of malaria cases and 93% of malaria deaths [3]. In India during 2005, there were 1.8 million reported cases of malaria with 940 deaths. There was 0.7 million cases of falciparum malaria. In April 1953, Govt. Of India launched national malaria control programme (NMCP) which was operated successfully for 5 yrs. The incidence of malaria dropped down from 75 million in 1953 to 2 million cases in 1958. In 1958 Govt of India launched the NMEP which was operated successfully till 1961. According to WHO (2000), the commonest complication of p.falciparum infection in children are cerebral malaria, anemia, respiratory distress and hypoglycaemia, & other form of complication includes renal failure, electrolyte imbalance, shock, black water fever and spontaneous bleeding[4]. With this rationale, the present study was carried out with the aim to establish the incidence of p.falciparum malaria in children and different spectrum of complications in falciparum malaria in Bihar.

Materials & methods

Longitudinal cohort study was carried out between Oct 2005 and Sept 2006 in the Department of PMCH, Patna. All children upto 18 yrs of age with fever of short duration visited to hospital either in OPD or indoor without any documented pre-existing systemic illness were included in this study. The cases for present study were selected on random basis amongst the case of malaria as per following protocol.

1. Primary pool- patients of all age groups, religion, presented with fever of short duration without any documented pre-existing illness and tested for malaria parasite via PBS (thick & thin smear) and rapid antigen test.
2. Secondary pool- cases from primary pool with definite diagnosis of p. falciparum malaria were further divided into uncomplicated & complicated group according to WHO criteria 2000.

Relevant investigations done were: CBC, renal profile- blood urea, serum creatinine; liver function test- serum billirubin, SGPT & SGOT, alkaline phosphatase, prothrombin time; blood sugar (random); serum fibrinogen & FDP; serum electrolytes- Na^+, K^+, HCO_3^-; X-ray chest (PA view) and CT scan of brain (where needed). Final pool- those cases with p. faclciparum either complicated or uncomplicated as per inclusion criteria were finally selected for present study.

Results

Table 1: Demographic and clinical characteristics among febrile children

Characteristics	Number (%)
Total no. of febrile children which were examined	18700
Total no. of children suffering from malaria	937 (5.01%)
Total no. of malaria cases in which p.vivax was positive	787 (84%)
Total no. of malaria cases in which p.falciparum was positive	150 (16%)
This table shows the incidence of p.facliparum in febrile children was 0.8% and incidence of p.facliparum in out of total malaria cases was 16%	

Incidence of p. falciparum malaria among febrile children was 0.8%. Incidence of p. falciparum was 16% of total malaria cases. Incidence of p. falciparum in febrile male children 60% was more than female febrile children 40%. Incidence of p. falciparum in Hindu febrile children (80%) was more than Muslim children [Table 1]. Among the p. falciparum positive cases complicated cases were 43.5% and uncomplicated cases were 56.67%. The commonest age group of p. falciparum was in between 5-10 yrs (40%), followed by in <5 yrs (29%), in 10-15 yrs (25.33%) and >15 yrs (5.67%) [Table 2]. Cerebral anemia was commonest complication (29.23%) of p. falciparum infection followed by jaundice (29.2%), hypoglycaemia (29.2%), and severe anemia (24.6%). MODS (21.33%), ARDS (3.07%), shock (3.07%), DIC (1.5%), acidosis (4.61%), ARF (6.15%) were uncommon complications [Table 3].

Table 2: Age, sex and complicated or uncomplicated distribution of p.facliparum cases [n=150]

Age groups	No. of cases	Percentage
<1 yr	3	2%
1-5 yrs	40	27%
5-10 yrs	60	40%
10-15 yrs	38	25.33%
>15 yrs	9	5.67%
Male	90	60%
Female	60	40%
Complicated	65	43.33%
Uncomplicated	85	56.67%

Table 3: Different types of p.falciparum malaria complications

Types of complications	No. of cases	Male	Female
Cerebral malaria	19 (29.23%)	13 (68.42%)	6 (31.58%)
Hepatitis with jaundice	19 (29.23%)	11 (57.89%)	8 (42.11%)
Severe anemia	16 (24.61%)	7 (43.75%)	9 (56.25%)
Hypoglycaemia	19 (29.23%)	11 (57.89%)	8 (42.11%)
Shock	2 (3.07%)	1 (50%)	1 (50%)
ARDS	2 (3.07%)	2 (100%)	0
DIC	1 (1.53%)	0	1 (100%)
Acidosis	3 (4.61%)	2 (66.6%)	1 (33.94%)
ARF	4 (6.15%)	2 (50%)	2 (50%)
MODS	14 (21.53%)	8 (57.14%)	6 (42.86%)

Discussion

Out of 18700 febrile children, 937 (5.01%) were diagnosed as malaria. Out of 937 cases of malaria 150 (16%) were proved to be suffering from p.falciparum infection. Out of 150 cases of p.falciparum 65 cases (43.33%) were complicated according to WHO 2000 criteria and remaining 85 cases (56.7%) were uncomplicated. Incidence of p. falciparum malaria among febrile children was 0.8%. Incidence of p. falciparum was 16% of total malaria cases. Incidence of p. falciparum in febrile male children 60% was more than female febrile children 40%. Incidence of p. falciparum in hindu febrile children (80%) was more than muslim children [Table 1].Chandramohan et al (2001) had studied of 1945 children with fever and found 139 (7%) cases of malaria in which 22 cases (1.13%) were diagnosed as p.falciparum[5].The best-performing algorithms were a score of 4 clinical features in children (sensitivity 60.0% and specificity 61.2%) and a score of 5 in adults (sensitivity 54.6% and specificity 57.5%). The clinical features differed and algorithm performances were poorer than in previous studies in highly endemic areas. The conclusion is that malaria diagnosis in areas of low endemicity requires microscopy to be accurate [5]. In the present study the commonest age group of p. falciparum was in between 5-10 yrs (40%), followed by in <5 yrs (29%), in 10-15 yrs (25.33%) and >15 yrs (5.67%). After 15 yrs of age incidence of p.falciparum in febrile children was low because after 15 yrs of age less number of patient had come to paediatrics department. Gomber Sunil et al showed incidence of malaria in between 103 yrs (8.08%), in between 4-6 yrs (25.25%), in between 7-9 yrs (38.38%) and 10-12 yrs 28.28% respectively[6]. Age distribution among various age groups was 33.9% in 0–5 years, 30.1% in 5–10 years, and 30% in >10 years, which was almost similar in all age groups.A study done in East Delhi studied population of 1 to 12 years which shows 59.7% males and 40.3% females having P. vivax malaria, as compared to our study which shows 69% males and 31% females having P. vivax malaria in similar age group of 1 to 12 years[6]. Plasmodium vivax is traditionally known to cause benign tertian malaria, although recent reports suggest that P. vivax can also cause severe life-threatening disease analogous to severe infection due to P. falciparum. There are limited published data on the clinical and epidemiological profiles of children suffering from 'severe malaria' in an urban setting of India. To assess the clinical and epidemiological profiles of children with severe malaria, a prospective study was carried out by Kaushik JS et al[7] during June 2008-December 2008 in the Department of Pediatrics, Guru Teg Bahadur Hospital, a tertiary hospital located in East Delhi, India. Data on children aged < or = 12 years, diagnosed with severe malaria, were analyzed for their demographic, clinical and laboratory parameters. All patients were categorized and treated as per the guidelines of the World Health Organization. In total, 1,680 children were screened for malaria at the paediatric outpatient and casualty facilities of the hospital. Thirty-eight children tested positive for malaria on peripheral smear examination (2.26% slide positivity rate). Of these, 27 (71%) were admitted and categorized as severe malaria as per the definition of the WHO while another 11 (29%) received treatment on outpatient basis. Most (24/27; 88.8%) cases of severe malaria (n=27) were infected with P. vivax. Among the cases of severe malaria caused by Plasmodium vivax (n=24), 12 (50%) presented with altered sensorium (cerebral malaria), seven (29.1%) had severe anaemia (haemoglobin <5 g/dL), and 17 (70.8%) had thrombocytopaenia, of which two had spontaneous bleeding (epistaxis). Cases of severe vivax malaria are clinically indistinguishable from severe falciparum malaria[7]. Kaushik JS et al study[7] demonstrated that majority (88.8%) of severe malaria cases in children from Delhi and adjoining districts of Uttar Pradesh were due to P. vivax-associated infection. P. vivax should, thus, be regarded as an important causative agent for severe malaria in

children. In the present study showed 60% of the male and 40% of the female p.falciparum infected cases. Incidences of malaria in male more because they are frequently indulge in outdoor activities and so they are more exposed to mosquito bites. On the other hand female indulge indoor activities and better clothed than male, so they are less exposed to mosquito bites**[8].** Kochar et al. found similar results in their study with 33.0% females affected among cases of P. vivax malaria**[9].**In the present study among the p. falciparum positive cases complicated cases were 43.5% and uncomplicated cases were 56.67%. Nonimmune patients with P. falciparum malaria should be treated as a medical emergency and be considered for hospital admission, regardless of disease severity at presentation. Severe anemia is more common in children in highly endemic areas due to repeated or chronic Plasmodium infections. Thrombocytopenia is common, but usually not associated with bleeding. Disseminated intravascular coagulation is reported in fewer than 10% of patients with severe malaria**[10].**In the present study cerebral anemia was commonest complication (29.23%) of p. falciparum infection followed by jaundice (29.2%), hypoglycaemia (29.2%), and severe anemia (24.6%). MODS (21.33%), ARDS (3.07%), shock (3.07%), DIC (1.5%), acidosis (4.61%), ARF (6.15%) were uncommon complications [Table 3]. Cerebral malaria is the most common clinical presentation and cause of death in adults with severe malaria. The onset may be dramatic with a generalized convulsion, or gradual with initial drowsiness and confusion, followed by coma lasting from several hours to several days. The strict definition of cerebral malaria requires the presence of P. falciparum parasitemia and the patient to be unrousable with a Glasgow Coma Scale score of 9 or less, and other causes (e.g. hypoglycemia, bacterial meningitis and viral encephalitis) ruled out[11].The mortality of cerebral malaria ranges from 10% to 50% with treatment. Most survivors (>97% adults and >90% children) have no neurologic abnormalities on hospital discharge[12].Pulmonary edema is usually noncardiogenic and may progress to acute respiratory distress syndrome (ARDS) with an increased pulmonary capillary permeability. Volume overload and hypoalbuminemia may aggravate pulmonary capillary leakage. Chest radiograph abnormalities range from confluent nodules to basilar and/or diffuse bilateral pulmonary infiltrates. Noncardiogenic pulmonary edema rarely occurs with P. vivax and P. ovale malaria[13].Hypoglycemia is a common feature in patients with severe malaria. It may be overlooked because all clinical features of hypoglycemia (anxiety, dyspnea, tachycardia, sweating, coma, abnormal posturing, generalized convulsions) are also typical of severe malaria itself. Hypoglycemia may be caused by quinine- or quinidine-induced hyperinsulinemia, but it may be found also in patients with normal insulin levels. Most patients with shock exhibit a low peripheral vascular resistance and elevated cardiac output. Cardiac pump function appears remarkably well preserved despite intense sequestration of parasitized erythrocytes in the microvasculature of the myocardium. Postural hypotension may be secondary to autonomic dysfunction. Severe hypotension can develop suddenly, usually with pulmonary edema, metabolic acidosis, sepsis, and/or massive hemorrhage due to splenic rupture or from the gastrointestinal tract[10].A prospective study done by N. Mohanty et al revealed 216 children with complicated falciparum malaria showed hepatopathy in 33.3% of cases with a higher incidence in children aged above five years. Bilirubin and alanine aminotransferase were moderately raised in most cases. No significant association with other common complications and no higher risk of mortality were observed[14]. Indications for hospitalization include cerebral malaria, severe anaemia, haemoglobinuria, renal failure, pulmonary oedema, coagulopathy, severe thrombocytopenia, shock, high parasitaemia, metabolic acidosis, hypoglycaemia, intractable vomiting, dehydration, seizures, or altered level of consciousness[15]. Thrombocytopenia is associated with high parasitaemia levels, lower age, low Hb levels, increased MPV and platelet aggregate flag. Jaundice (30–50%) and raised liver enzymes (25–40%) are also relatively common but not usually associated with an adverse outcome[16].Respiratory distress was present in 17.7% (14/79) and 10.8% (7/65) children having P. falciparum and P. vivax infections, respectively. Among children in 0–5 year age group this proportion was 2% (1/50) and 14.6% (6/41), whereas in 5–10 year age group it was 12.6% (12/95) and 2.3% (1/44) and in > 10 year age group it was 2.5% (1/40) and 0% (0/18), respectively. Hepatic dysfunction was present in 44.3% (35/79), 26.2% (17/65), and 16.7% (1/6) children having P. falciparum, P. vivax, and mixed infections, respectively. Among children in 0–5 year age group this proportion was 16% (8/50), 36.6% (15/41), and 16.7% (1/6), whereas in 5–10 year age group it was 25.3% (24/95), 2.3% (1/44), and 0% and in > 10 year age group it was 7.5% (3/40), 5.6% (1/18), and 0% (0/2), respectively[9]. The mortality in severe P. vivax malaria was recorded in 6.15% (4/65) children, whereas the same in severe **P. falciparum** was observed in 7.59% (6/79) children. Thus, **P. vivax** infection was found to be almost equally serious

to cause significant mortality in comparison to **P. falciparum**[9].

Conclusion

Malaria should be included in the differential diagnosis of every febrile illness in a person with a history of travel to a malaria-endemic area. Delays in recognition and appropriate treatment of malaria increase morbidity and mortality. The major complications of severe malaria include cerebral malaria, pulmonary edema, acute renal failure, severe anemia, and/or bleeding. Any of these complications can develop rapidly and progress to death within hours or days. Light microscopy of blood smears is the standard method for diagnosing malaria, although new and promising nonmicroscopic diagnostic methods are under development. All patients with severe malaria should receive parenteral treatment immediately. During our study, it was observed that p.falciparum malaria accounts for good number of cases among febrile children. It should be screened for any child presenting with fever along with hepatomegaly and or spleenomegaly to diagnose as early as possible. Once diagnosed p.falciparum malaria, should be treated and manged urgently and appropriately to prevent dreaded complications, so that mortality and morbidity due to complicated malaria could prevented or decreased.

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