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Pediatrics

CLINICAL, LABORATORY PROFILE AND OUTCOME OF RDT POSITIVE PATIENTS OF MALARIA IN CHILDREN

Mandraha Shipra M.D. Paediatrics, Senior Resident, GMC Bhopal.

Randa Rashmi M.D.Paediatrics, Assistant Professor, GMC Bhopal. - Corresponding Author

Nadkarni Jayashree M.D.Paediatrics, Professor, GMC Bhopal.

ABSTRACT Introduction: Malaria is a major public health problem of developing countries. Though the incidence is on the decline, but delay in diagnosis can increase the severity and complications of the disease.

Aim: The study aimed to document the clinical and laboratory profile of malaria in paediatric patients and to study the complications. It's an observational cross sectional hospital based study done at a teaching hospital in Central India over 15 months.

Results: Out of 95 patients (diagnosed by Rapid diagnostic kit), 18(18.8%) had P.vivax, 66 (69.4%) had P.falciparum and 11 (11.5%) had mixed malarial infections. Majority of them i.e.31(32.6%) presented with severe malarial anemia. Cerebral malaria was seen in 30 patients(31.5%), 20 cases (21 %) presented with shock requiring ionotropic support, 66 (69%) patients received blood transfusion and all the 10(10.5%)patients who expired, had cerebral malaria. Majority of deaths were due to P. falciparum malaria.

Conclusions: Malaria has significant morbidity and mortality. Early diagnosis, management and referral, if necessary, can be done to prevent morbidity and mortality due to malaria.

KEYWORDS : Malaria, Rapid Diagnostic Test, Cerebral malaria, Children

Introduction

Malaria is a mosquito-borne, lethal disease that affects millions and kills hundreds and thousands of people each year; mostly children. India is endemic for malaria with unstable transmission inhibiting the development of immunity and predisposing all age groups to the disease. Children under five are the greatest sufferers with maximum mortality. P. falciparum and P. vivax cause majority of cases. It is transmitted to humans through the bites of infected female Anopheles mosquito and symptoms usually appear 7 days or more after the bite. It is an acute febrile illness, manifesting clinically as fever, headache, decreased appetite, lassitude and pain in limbs. If not treated on time, it can progress to severe illness and complications, often leading to death. In all suspected cases parasitological diagnosis should be confirmed before starting the treatment. Microscopy of blood smears is the gold standard for diagnosis. Malaria RDTs are designed for malaria endemic areas beyond the reach of good-quality microscopy. In other situations, such as a very busy facility to reduce turn around time.

About 3.2 billion people – almost half of the world's population, are at risk of malaria. According to the latest WHO estimates, released in 2016, there were 212 million cases of malaria in 2015 and 429 000 deaths [1]. Around 1.13 million cases and 287 deaths of malaria have been reported in India in 2015 [2]. In areas with high transmission of malaria, children under five years are particularly susceptible to infection, illness and death. More than two thirds (70%) of all malaria deaths occur in this age group. Malaria incidence and mortality rates has fallen globally by 22% and 50% respectively since 2000[1]. Though the incidence is on decline, malaria still continues to be a major health problem. Madhya Pradesh, in central India, is one of the worst affected states with API of 1.26 and P.falciparum rate of 43% [2]. Paediatric population is especially vulnerable to this preventable and curable illness. The present prospective study was undertaken to assess the clinical course, complication, outcome and prognostic indicators, if any, of malaria in children in a tertiary care centre of central India, Bhopal.

Subjects and Methods: This observational cross sectional study was conducted in Department of Paediatrics, Gandhi Medical College, Bhopal from August 2014 to October 2015. The hospital is a government tertiary care hospital. We receive patients from central India with almost a 100 children of malaria admitted every year. A total of 95 inpatients under 12 years of age, presenting with fever with or without chills and rigors, headache, vomiting, or having features suggestive of malaria and being RDT positive for P. falciparum, P. vivax or both were included in the study. Clearance was obtained from the institutional ethics committee. The study protocol was fully explained to the parents and informed consent was taken.

Details of the patients and the demographic profile including name, age, gender, residential address etc were noted. All details of history and thorough clinical examination were entered in a predesigned proforma. The patients were tested by One Step Malaria HRP-II (P.f) and pLDH(P.v) Antigen Rapid Tests supplied by Government of India under NVBDCP. These RDTs are used for detection of Plasmodium falciparum histidine-rich protein-II and Plasmodium vivax lactate dehydrogenase antigens. Relevant laboratory investigations were done. Definition given by WHO was used to label as severe malaria and treatment was given as per WHO guidelines [3]. The outcome was assessed in all patients.

Data collected was analyzed using SPSS 20 and Microsoft Excel 2010. The qualitative data were expressed in proportion and percentages and quantitative data expressed as mean and standard deviations. The difference in proportion was analyzed by using chi square test and the differences in means were analyzed by using student T test (unpaired). Significance level for tests was determined as 95%. Test was considered significant if p value <0.05.

Results: During study period, a total of 95 patients who were RDT positive for malaria were included in this study. Out of these, 66 (69.4%) were positive for P. falciparum, 18 (18.8%) for P. vivax and 11 (11.5%) were positive for both P. vivax and P. falciparum. There was slightly higher male preponderance with 56 (59%) males and 39(41%) females. Maximum number of cases encountered, were in the age group of more than five years. There were 30 patients (31.6%) in the age group 0-4 years, 36 patients (37.8%) in the group 5-8 years and 29 patients (30.6%) above eight years of age. Mean age calculated was 6.7 ± 3.39 years. 50% cases in vivax group were below four years of age where as in falciparum group 32% were of age below four years. 48 (50.6%) patients were referred from other health centres, the remaining 47 (49.4%) presented directly to the department. A total of 58 (61.0%) patients belonged to rural areas, rest 37 (39.0%) were residents of urban areas.

All the cases (100%) presented with fever of short duration with two third cases having chills and rigors also. Other major presenting symptoms in this study were headache, vomiting, abdominal pain, convulsions or altered consciousness, jaundice and hematuria. Vomiting was found to be more common in patients of more than five years of age which is statistically significant (p value 0.009). There was no statistically significant difference in the clinical presentation of different malarial species (Table no 1).

On physical examination, pallor was a significant finding present in 88.4% (n=84). Icterus was found to be more common in falciparum malaria in 22.6% patients (15/66) and only one patient of vivax malaria had Icterus. Hepatomegaly and hepatosplenomegaly was also seen more in P.falciparum malaria and is statistically significant. Splenomegaly was present in 63.6% patients but there was no statistically significant difference in this finding between falciparum, vivax or mixed malaria groups. (Table no 2)

As per the complications, severe malarial anemia and cerebral malaria were the commonest ones requiring hospitalization. 30 patients had cerebral malaria while 31 patients had severe anaemia. 30 patients (31.5%) had neurological dysfunction in the form of altered sensorium, loss of consciousness and generalized convulsions. Out of these 30 patients, 20(66.8%) cases were falciparum positive, 5 (16.6%) patients had vivax malaria and 5 (16.6%) patients had mixed infection. Hypoglycaemia was reported in only one patient who was positive for falciparum. 20 patients (21%) presented with shock requiring ionotropic support, though the value was not statistically significant (p value 0.92) (Table no 3).

Out of 95 RDT positive malaria cases, peripheral smear was positive in 29 (30.5%) patients only. As per laboratory tests, 31 (32.6%) cases had haemoglobin value less than 5 gm/dl and thus had, according to WHO criteria, severe malarial anemia. Mean haemoglobin level was 6.58 +- 2.18 g/dl. Thrombocytopenia was a significant finding present in 77.8% patients (n=74). Mean platelet count was 101 thousands/mm3 (range from 20 to 280 thousands/mm3). Severe thrombocytopenia (platelet count < 50,000) occurred in 23 patients (24.2%). A creatinine value of more than 3 mg/dl is considered as renal impairment in malaria as per WHO criteria. In this study, three patients (3%) had renal impairment, all were positive for P.falciparum. Serum bilirubin of >3 mg/dl was found to be present in 27.3% (26/95) patients, majority of them were P.falciparum positive (Table no 1).

As regards the outcome, out of 95 patients, 74 patients (77.8%) were successfully discharged with appropriate treatment as per WHO guidelines. Mean duration of stay was 5.2 days in cases of P. vivax malaria, 8.7 days in P. falciparum malaria and 8.9 days in mixed malaria. As regards stay, p value was statistically significant for falciparum patients (p< 0.001) indicating that they required significantly longer duration of hospitalization. There were 10 mortalities (10.5%) due to malaria, out of which 7 deaths (70%) were due to P. falciparum malaria. Mixed group has 18.2%, falciparum group 10.6%, and vivax group has least 5.5% mortality rate. Out of 30 cases of cerebral malaria, there were 10 deaths. All the deaths were due to cerebral malaria.

Significant association was there between cerebral malaria and mortality (p value 0.002). Factors associated significantly with mortality as per the study were cerebral malaria (Odds Ratio :110.2, 95% confidence interval : 12.2-165.3) and shock (Odds ratio : 60.5, 95% confidence interval : 6.9-112.6)(Table no 4).

Discussion: Malaria is among the prevalent infectious disease in developing world including India and a leading public health problem. Also infants and young children can have atypical presentation and are identified as high risk groups as they have more chances to develop severe malaria. This study was conducted on a prospective basis from October 2014 to December 2015. A total of 95 cases of malaria diagnosed by RDT were included. Most of the cases i.e. 85% of total malaria cases were admitted between September and December supporting the seasonal variation of malaria incidence in this region. Other studies from central and southern India by Wasnik PN et al (2012) and Mary Anne et al (2014), also shown seasonal variation, but peak was seen during monsoon season i.e. between July and September [4][5].

P. vivax infection was present in 18 patients (18.8%), P. falciparum in 66 patients (69.4%), while 11 patients had mixed infection with both P. vivax and P. falciparum. Maximum numbers of hospitalization were due to P. falciparum malaria, reflecting P. falciparum as major cause of morbidity. This is consistent with the recent trend of malaria in our country as reported by NVBDCP with upsurge in falciparum cases during last few years with easy availability of bivalent RDTs as one of the contributing factor [2]. Previously most of the studies had shown P.vivax as major cause of malaria [6][7][8]. And few had similar parasitic profile as of this study [9].

Malaria affects all ages and both sexes, but in present study it was more common in males (n=56). Male: female ratio among cases was 1.4:1 coincides with the fact that male children are usually less covered and exposed more to mosquito bites. The study results are in conformity with what was reported earlier by studies done in different parts of India [7] [8] [9]. 61% population was from rural areas. About half of the patients were referred from nearby peripheral health centers, while the rest presented directly at the tertiary level care centre. Most of the patients, who had major complications, were referred from other health centers, suggesting the possible role of delayed diagnosis in development of major complications. 60% patients were presented within 5 days of onset of symptoms. The most common presenting complaint was fever which was present in all i.e. 100% cases and it is similar to what it had been observed in previous studies done by Taksande et al [10] and Kaushik et al [7]. Fever was associated with chills and rigors in 60% patients i.e. 61% in vivax, 65% in falciparum and least 27% in mixed infection. Headache and vomiting was present in 30.5% patients. After comparing the presentation in different age groups, it was found to be statistically significant (p value <0.009) in children above five year age group. Hematuria/oliguria was the least common presentation seen in only 8.4% cases. Both falciparum and vivax malaria cases were presented with similar symptom profile in children. A study from Colombia comprising mainly of adult population also reports symptoms presented with similar distribution for both parasite species in uncomplicated malaria [11]. Also a study on children from northern India showed similar results of clinical presentation [6].

In our study, over all 66.3% patients had hepatomegaly, 56.8% had splenomegaly and 48.8% had hepatosplenomegaly on examination. On statistical analysis, hepatomegaly was significantly more common in P.falciparum malaria (74.2 %,) as compared to P.vivax malaria (44.4%) p value being 0.012 and also hepatosplenomegaly found to be commoner in P.falciparum with p value 0.023. As compared to common belief that splenomegaly is an important finding in patients with malaria, in present study it was found that hepatomegaly as well as hepatosplenomegaly both was a significant finding in patients with falciparum malaria.

Severe malarial anemia and cerebral malaria were the commonest complications requiring hospitalization. P.falciparum remains a major cause of cerebral malaria. Convulsion (27.7%) was more common than headache (22.2%) in vivax malaria, but falciparum cases had equal frequency of both these complaints. 30(31.5%) patients had cerebral malaria in this study. It was present in varied but significant number of patients in other different studies as well with 50% in a study by Kaushik et al [7], 20.7% in Mittal et al study [6], 10% in Kashinkunti et al study [12]. Though total number of cases of cerebral malaria was more in falciparum group, proportion of cases was almost similar in both vivax and falciparum group. Mittal et al conducted a study on malaria in children in northern India. Out of 198 cases included, 64.6% patients had P. vivax malaria out of which, 12.5% patients had cerebral malaria and 25.8% had severe anemia [6]. Anemia has been widely observed in both vivax and falciparum malaria. Severe malarial anemia was present in 32.6% of our patients. Kaushik et al showed similar (29.1%) results [7]. In present study, severe malarial anemia was more common in the falciparum group than the vivax group but is not statistically significant. 66 patients had received blood transfusion. Comparing both groups, requirement of blood transfusion was found to be more in P.falciparum infection and is statistically significant (p value 0.002). The probable mechanisms contributing to malarial anemia can be increased destruction of parasitized and un-parasitized erythrocytes (immune-mediated lysis, phagocytosis, splenic sequestration) and decreased RBC production (dyserythropoiesis and bone marrow suppression, inadequate reticulocyte production, effects of inflammatory cytokines, effects of parasite factors)[13].

Renal impairment as per WHO criteria of severe malaria with serum creatinine >3 mg/dl or urea > 20 mmol/ occurred in three patients with all of them having P.falciparum malaria and one patient required peritoneal dialysis. Though acute kidney injury defined by KDIGO was seen in 11 patients (11.6%), out of which 9 patients were P.falciparum positive. The incidence of renal impairment was less in the present study compared to other studies. A study done on 178 children with malaria had 45.5% AKI cases [14].

Other complications included thrombocytopenia (< 1.5 lac) which occurred in a significantly high number i.e. 74 out of 95 (77.8%)

patients. Similar results were shown by others also [12][15]. Severe thrombocytopenia (platelet count < 50000) occurred in 23 patients (24.2%) with 20 patients with severe thrombocytopenia were falciparum cases, and rest 3 had mixed infection. The pathogenesis of malaria thrombocytopenia is complex and may be related to coagulation disturbances, splenomegaly and platelet destruction by macrophages, bone marrow alterations, antibody-mediated platelet destruction, oxidative stress and platelets aggregation [13]. Jaundice was found in 27.5% cases, more commonly in falciparum and mixed group.

Out of 95 cases in our study, there were 10 deaths and mortality rate was found to be 10.5%, 70% of which was due to P.falciparum malaria. Among vivax and falciparum group, mortality was 5.5% and 10.6% and respectively, being more in the falciparum group. Another study done by Mittal et al in children showed similar results [6].

Mean duration of hospital stay was 5.2 ± 1.6 days for P.vivax malaria, 8.7 ± 2.1 days for P.falciparum infection and 8.9 ± 2.4 days for mixed malaria with p value was statistically significant for falciparum malaria requiring longer duration of hospitalization. There was no statistically significant difference found between duration of stay and mortality (p value 0.063). Though the number of patients referred from other peripheral health centers were equal to the number of those presenting directly to the tertiary care centre, it was found in the study that all the patients who expired were referred from peripheral centers. Thus, emphasizing the need of early diagnosis, initial management and early referral of severe malaria children to be done at the first contact with health facilities to improve outcome.

Mortality was significantly associated with cerebral malaria (p value 0.002, which is similar to other studies. 33.3% children having cerebral malaria died. Odds ratio calculated was 110.2 with 95% CI of 12.2-165.3. Shock was also found to be significantly associated with mortality, seen in 9 out of 10 deaths with p value 0.014, OR – 60.5, 95% CI – 6.9-112.6. These findings were in concordance with other studies including one by Krishnan et al. In this study, 56% mortality was due to cerebral malaria [16]. In our study, out of 10 deaths, 3 patients had severe malarial anemia, thrombocytopenia was present in 5 patients. Liver functions were deranged in 2 patients, while 4 patients had deranged renal functions. Multi organ dysfunction was found to be more common than a single organ involvement as was suggested by another study [17].

To conclude, malaria, if diagnosed and managed early and referred timely whenever necessary, can prevent a lot of morbidity and mortality in the vulnerable pediatric population. It is important to follow recommendations diligently to decrease morbidity and mortality due to malaria and to avoid the problem of drug resistance. The gains of the past decade should be scaled up to make malaria elimination and eradication a reality.

Table no.1- Clinical and laboratory features of P vivax, P falciparum and mixed malaria infection

Symptom	P.vivax (n=18)	P.falciparum(n=66)	Mixed(n=11)	Total(n=95)
Fever	18(100%)	66(100%)	11(100%)	95 (100%)
Chills and rigors	11(61%)	43(65.1%)	3(27.2%)	57(60%)
Headache and vomiting	4(22.2%)	21(31.8%)	4(36.3%)	29(30.5%)
Convulsions	5(27.7%)	21(31.8%)	4(36.3%)	30(31.5%)
Hematuria/oliguria	2(11.1%)	6(9%)	0(0%)	8(8.4%)
Haemoglobin <5 g/dl	4(22%)	24(36%)	3(27%)	31 (32.6%)
Platelet count <1.5 lac	13(72%)	54(82%)	7(64%)	74 (77.8%)
Acute kidney injury	1(5.6%)	9(13.6%)	1(9.1%)	11(11.6%)
S.bilirubin >3mg/dl	3(17%)	18(27%)	5(45%)	26 (27.3%)

Table no. 2- Physical signs of malaria as per species

Sign	Vivax (n=18)	Falciparum (n=66)	Mixed (n=11)	Total (n=95)	p value
Pallor	14(77.8%)	60(90.9%)	10(90.9%)	84(88.4%)	0.11
Icterus	1(5.6%)	15(22.7%)	2(18.2%)	18(18.9%)	0.16
Hepatomegaly	8(44.4%)	49(74.2%)	6(54.5%)	63(66.3%)	0.012 [significantly more in falciparum]
Splenomegaly	10(55.6%)	42(63.6%)	2(18.2%)	54(56.8%)	0.53
Hepato splenomegaly	4(22.2%)	35(53.03%)	2(18.18%)	41(48.80%)	0.023 [significantly more in falciparum]

Table no.3- Comparison of clinical charact eristics of severe malaria

Clinical characteristics	P.Vivax (n=18)	P.Falciparum (n=66)	Mixed (n=11)	Total (n=95)	p value
Cerebral Malaria	5(27.7%)	20(30.3%)	5(45.4%)	30(31.5%)	0.41
Severe anemia	4(22.2%)	24(36.3%)	3(27.3%)	31(32.6%)	0.25
Shock	4(22.2%)	14(21.2%)	2(18.2%)	20(21%)	0.92
Renal impairment	0(0%)	3(4%)	0(0%)	3(3.15%)	
Jaundice	3(16.7%)	18(27.3%)	5(45.5%)	26(27.4%)	0.25

Table no.4- Outcome of cases on the basis of complications

Complication	Death	Total	p value	Odds Ratio	95 % CI
Cerebral Malaria	10	30	0.002, significant	110.2	12.2-165.3
Severe anemia	3	31	0.23	0.87	0.2 – 3.6
Shock	9	20	0.014 significant	60.5	6.9 – 112.6

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