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Paediatrics

Clinical, Laboratory and Cardiovascular Manifestations in Pediatric Malaria

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ABSTRACT To study the incidence of complications and mortality due to P.vivax and P.falciparum malaria and analyze the sequelae of systemic manifestations, especially cardiovascular and its role as a predictor of significant morbidity and mortality in children. Materials and methods - It was a single centre, observational, cross sectional study of all children aged 6 months to 15 years. The study population included all patients admitted in the ward/ IPCU and OPD with slide/rapid antigen test positive for malaria. Details of the patient including age, sex, address and religion were noted. Detailed general and systemic examination was carried out. CBC,LFT, RFT were the investigations noted. The patient was staged according to parasitic index on peripheral smear. Every patient underwent X-Ray chest, ECG and 2D Echo/colour Doppler evaluation. Results – Fever was universal finding in all patients. Spleen was involved in 100% cases of mixed malaria. P. vivax malaria was the commonest malaria found in children followed by P. falciparum. Statistically significant results obtained in Chest X-ray ($p<0.032$) and 2 D echocardiography ($p <0.016$). Conclusion - Complications of malaria are significantly higher in cases of P. falciparum monoinfection. P. falciparum monoinfection has emerged as single significant cause of cardiac morbidity in pediatric malaria patients. Morbidity though is severe its completely reversible on timely initiation of treatment.

KEYWORDS : P. Vivax, P. Falciparum, X ray chest, ECG, 2 D Echo.

INTRODUCTION

Malaria has played a major role in human history, having caused more harm to people than any other infectious disease[1].

About 3.3 billion people live in areas at risk of malaria transmission in 106 countries and territories. The World Health Organization (WHO) estimates that in 2010, malaria caused 219 million clinical episodes and 660,000 deaths[2]. An estimated 91% of deaths in 2010 were in the African Region, followed by the South-East Asian Region (6%), and the Eastern Mediterranean Region (3%). About 86% of deaths globally were in children[3].

Malaria is of overwhelming importance in the developing world today as most malarial deaths occur in infants and young children[4].In endemic areas, children younger than age 5 years have repeated and often serious attacks of malaria[5]. The survivors develop partial immunity. Thus, older children and adults often have asymptomatic parasitemia.

The main aim of antimalarial treatment in children, which is also the basis of National Antimalarial Program, is to prevent early morbidity and death by early diagnosis and prompt treatment[6].

The two major human malaria species in India are Plasmodium falciparum and P. vivax; P. malariae has been reported in the eastern India state of Orissa, while P. ovale is extremely rare.

Cardiac involvement in malaria has not been studied widely. There have been very few reports of experimental and postmortem studies indicating myocardial involvement in malaria. In Southeast Asia, few studies have been done on cardiac involvement in malaria in pediatric patients. Cardiac involvement is very rare and seems to be limited to acute infection with Plasmodium falciparum[7].

Diagnosis of malaria in our country is mainly based on symptoms due to lack of proper infrastructure. As per antimalarial drug policy, all fever cases, both in high risk and low risk areas, without any other symptoms are to be treated with antimalarials. The indiscriminate use of antimalarials is leading to drug resistance. However, in complicated malaria or malaria with danger signs, presumptive treatment may be started before confirmation. Although the peripheral blood smear examination has been the "gold standard" for the diagnosis of malaria, the immune-chromatographic tests like "Rapid diagnostic test" for the detection of malaria antigens, developed in the past decade, have opened a new and exciting avenue in malaria diagnosis[8].

This study becomes important due to the fact that cardiovascular manifestations are responsible for major morbidity in malaria in children and mortality is decreasing due to advanced care and early initiation of treatment.

MATERIALS AND METHODS

Aims and Objectives:

1) To study the emerging trends of malaria, its systemic manifestations and response to therapy in children.
2) To study the incidence of complications and mortality due to P.vivax and P.falciparum malaria.
3) To analyse the sequele of systemic manifestations, especially cardiovascular and its role as a predictor of significant morbidity and mortality.

This study was performed over a period of 1.5 year from April 2011 to Oct 2012.

It involved 88 cases who were diagnosed malaria and satisfied the inclusion criteria, attending the OPD, ward, PICU and EPR.

The inclusion criteria were as follows:

1) Patients of pediatric age group (6 months-15 years) with Slide positive / rapid antigen test positive for malaria, done in the hospital or from outside laboratory.

The exclusion criteria were as follows:

1) Patients of suspected malaria but negative slide / Rapid antigen test.
2) Patients with underlying congenital / acquired heart disease.

It was a single centre, observational, cross sectional study of all

children aged 6 months to 15 years, attending an outpatient department (OPD) or admitted in the ward or pediatric intensive care unit (PICU) or emergency pediatric room (EPR) of a tertiary care centre in Mumbai with malarial parasite on peripheral smear examination or by rapid antigen test. Suspected patients with negative slide / rapid antigen test and those patients with underlying congenital / acquired heart disease were excluded from the study.

The patients were enrolled after taking an informed parental consent. Details of the patient including age, sex, address, religion were noted. Detailed general and systemic examination was carried out in all. The various lab investigations were entered. The patient was staged according to parasitic index on peripheral smear. Every patient underwent X-Ray chest, ECG and 2D Echo/ colour doppler evaluation.

Following parameters were evaluated during the study:
Heart Rate – Normal values of heart rate as per the reference range given for the corresponding age[9].

Blood pressure – Normal values of blood pressure centiles for systolic blood pressure (SBP) and diastolic blood pressure (DBP) according to height, sex, and age are given for boys and girls. Blood pressure less than 50th centile considered as hypotension[10].

Laboratory parameters like Hemoglobin, TLC, SGOT/SGPT, Serum bilirubin, and serum BUN/creat were evaluated as per the normal reference given for the corresponding age and sex[11].

Platelet count- Normal platelet count is 1,50,000-4,00,000/mm^3 and considered thrombocytopenia as platelet count below 1,50,000[12].

Sample collection was done as soon as malaria was suspected. Collection was done before the administration of anti-malarials which causes detection of parasites difficult due to its morphologic alteration. Smear was prepared soon after collection which enables better adherence of films to the slide and causes minimal distortion of parasites and red cells. In blood sample collected with anti-coagulants, the film was prepared within 2 hours for best results[13].

Smear was examined with 100x oil immersion objective. A minimum of 100 fields were examined before concluding the slide to be negative. Once negative,sample was examined for at least 3 consecutive days where clinical suspicion of malaria was strong.

The parasite index was utilized to determine the severity of malaria along with prognosis and assessing the response to treatment. In a positive blood smear for malarial parasite, parasitic index (PI) was derived by quantifying the parasite number per 1000 red blood cells (RBCs) in a thin smear and dividing it by 10 to get it in percentage[14]. Rapid diagnostic tests (Eg: OPTIMAL) are immune-chromatographic test (ICT) to detect plasmodium specific antigens in blood sample. Chest X- ray we performed by routine method in our tertiary care centre. We performed electrocardiography of all patients tested positive for malaria in our centre by BPL Cardiac 108T ECG machine.

2D - Echocardiography /Color Doppler was performed on all patients tested positive for malaria as a part of this study. The machine used for this study was iE33 (Philips), a stand-alone, state-of-the-art 2 D-echocardiography machine housed in a separate echocardiography room.

Statistical Analysis

The data was analysed and tabulated using the SPSS package, software version 16.0. Descriptive statistics were used for data presentation. Pearson Chi- square test was used to test significant difference in mean of variables between two groups.

RESULTS

The mean age of patients in study population was 5.33 years. The largest proportions of children were in the 6 months-5 year age group (64.77%). Males outnumbered females in present study with a ratio of 2.38. In present study, fever was the universal finding in all patients; followed in decreasing order by nausea and vomiting (27.3%), abdominal pain (17%), cough (6.8%), headache (5.7%), rash (2.3%) and altered sensorium (2.2%). Of 88 patients, 45 (51.13%) patients had tachycardia and 2(2.27%) patients had bradycardia. Blood pressure was normal in 75 (85.22%) cases; however, 13 (14.77%) patients had hypotension (< 50th percentiles for expected age and gender), of which 4 (4.54%) patients had blood pressure < 5th percentiles for expected age and gender. Hepatomegaly was present in 63 (71.6%) patients. Spleen was involved in 100% cases of mixed malaria, 48(75%) cases of P. vivax malaria and 13(72.2%) cases of P. falciparum malaria. Majority of present study population were anemic as seen in 57 out of 88 (64.77%), having a hemoglobin value of minimum 3.6 gm%. The lowest mean Hb of 7.15 gm% was found in cases of mixed malaria. Thrombocytopenia was seen in 72 patients (81%). Severe thrombocytopenia (< 20,000/mm^3) was found in 10 (11.36%) patients. Liver functions were also deranged in significant patients with relatively severe involvement in those with falciparum malaria.

In present study group, we diagnosed malaria by peripheral smear and optimal. On the basis of peripheral smear, P. vivax malaria cases were 69.31%, while P.falciparum were 17.04% and 4.54% of population suffered from mixed infection. On the basis of Optimal, P. vivax malaria cases were 68%, P. falciparum cases 24% while mixed malaria was found in 8% cases.

Chest X-ray showed cardiomegaly in 6.8% patients, while pleural effusion was present in 2.3% patients. Association between chest X-ray findings and type of malaria was statistically significant (p<0.032).

TABLE No. 1 : Showing association between Chest X ray and Type of Malaria.

X-Ray Chest	Type of Malaria				Total	Chi-Square Test	p-value
	No.	P. Vivax	P.Falciparum	P. Vivax and P. falciparum			
Cardiomegaly	No	2	4	6	6	9.968	P= 0.041
	%	3.1	22.2	6.5	6.8		
Pleural effusion	No	1	1	2	2		Significant at p <0.05 level
	%	1.6	5.6	2.3	2.3		
Normal	No	61	13	80	80		
	%	95.3	72.2	90.9	90.9		
Total	No	64	18	88	88		
	%	100.0	100.0	100.0	100.0		

Significant at p <0.05 level

ECG showed prolonged PR-interval as the most common abnormality seen in 10(11.4%) patients followed by prolonged PR and QRS intervals in 2(2.3%) patients. Bradycardia, prolonged PR and QRS interval were found in 1 patient (1.1%).

2 D-echocardiography was abnormal in 15 (17%) patients which was statistically significant (p < 0.016). Mild pericardial effusion was present in 4.5% patients while moderate and trivial pericardial effusion was present in 3.4% each. Mild TR was seen in 1(1.1%) patient while mild TR and MR were noted in 1(1.1%) patient. Systolic and diastolic dysfunctions were present in 14 (15.9%) patients. Mild LV dilatation was present in 9(10.2%) patients, while early diastolic dysfunction was present in 3 (3.4%) patients. Mild LV dilatation with early diastolic dysfunction was present in 2 (2.2%) patients.

Table No 2 : Showing correlation of 2 D Echocardiography with Type of Malaria.

2D Echo/ Colour Doppler	Type of Malaria				Total	Chi-Square Test	p-value
	No.	P. Vivax	P.Falciparum	P. Vivax and P. falciparum			
Abnormal	No	8	7	0	15	8.242	P= 0.016 Significant at p <0.05 level
	%	12.5	38.9	0.0	17.0		
Normal	No	56	11	6	73		
	%	87.5	61.1	100.0	83.0		
Total	No	64	18	6	88		
	%	100.0	100.0	100.0	100.0		

Significant at p <0.05 level

In present study, we found 44 (50%) patients responded to chloroquine while 50% patients required artimisinine combination therapy. 77(87.5%) patients responded to primary therapy, while 11(12.5%) patients who remained positive on PSMP and optimal after primary treatment required second line treatment.

All patients were discharged after treatment and there was no mortality due to malaria.

DISCUSSION

According to the World malaria report 2011, there were about 219 million cases of malaria (with an uncertainty range of 154 million to 289 million) and an estimated 660,000 deaths in 2010 (with an uncertainty range of 610,000 to 971,000). Malaria mortality rates have fallen by more than 25% globally since 2000, and by 33% in the WHO (World Health Organization) African Region. Most deaths occur among children living in Africa where a child dies every minute due to malaria[2]. Sharma et al (1983) found that malaria incidence in PHC Kichha in District Nainital (erstwhile in U.P.) and Kharkhoda in District Sonepat (Haryana) was much high 95% (1784 cases) and 97% (7117 cases)[15].

The mean age of the patients in present study was 5.15 years with a range from 6 months–15 years in case of P. vivax malaria, while it was 4.8 years in case of P. falciparum malaria and in mixed malaria, the mean age was 6 years. Shrivastava et al found peak incidence of severe malaria is in the age group of 5-9 years[16]. In present study, fever was the universal finding in all patients; followed in decreasing order by nausea and vomiting (27.3%), abdominal pain (17%), cough (6.8%), headache (5.7%) rash (2.3%) and altered sensorium 2 (2.2%). Hazra BR et al, found that continuous or remittent fever has been observed in 40% and 27.27% cases of P.falciparum and P.vivax respectively, while absence of classic paroxysms of fever, in association with splenomegaly when present posed a diagnostic difficulty with enteric fever in the same study[17]. A study carried out by Abdul Rasheed et al showed triad of fever, chills and sweating was present in 91% of subjects with all three varieties of P. infection[18]. In present study minimum hemoglobin was 3.6 gm%. Out of 88 patients, 32 patients (36.36%) had hemoglobin values between 5.1 to 8 gm%, while 2 patients (2.27%) had hemoglobin below 5 gm%.

In a study carried out by Marcela Echeverri et al, anemia was found in 39% of women and in 51% of men[19]. Abdul Rasheed et al found anemia and Jaundice were more common in P.falciparum and mixed infection as compared to P.vivax[18]. Mockenhaupt et al reported that severe anemia as the leading manifestation of severe malaria[20].

In present study, abnormal chest radiography was noted in 8 patients, of which 6 patients had cardiomegaly (6.8%) and 2 patients had pleural effusion (2.3%). Sirivichayakul C et al reported that an 11-year-old boy who suffered from cerebral malaria and massive right pleural effusion[21]. Frazen et al studied cardiac involvement during and after malaria and found that during the acute phase ECG abnormalities were common (5/22); pericardial effusion was found in 2 patients and global left ventricular hypokinesia in 1 patient infected with *Plasmodium falciparum*[22]. Yacoub et al examined 30 children with severe malaria and assessed their cardiac function by ejection fraction and left myocardial performance index which was mildly abnormal on admission compared with discharge[23]. In present study, 2 D echocardiography was abnormal in 15 (17%) patients while it was normal in 73(83%) patients. Laufer MK et al did research on 210 children between 6 months and 12 years of age with symptoms of malaria and found that chloroquine was effective at treating the malaria in 99 percent of the children studied[24].Stove KR et al reported that artemether-lumefantrine is a safe and effective treatment for children and adults with P. falciparum malaria[25].In present study, we found 44 (50%) patients responded to chloroquine while 50% patients required artimesinin combination therapy.

CONCLUSION

1) P. vivax monoinfection was the commonest malaria in children followed by P. falciparum monoinfection.
2) Fever was the universal finding in all children with malaria. Splenomegaly is the most common sign noted in cases of malaria.
3) Complications of malaria in the form of anemia, thrombocytopenia, liver and renal involvement is significantly higher in cases of P. falciparum monoinfection.
4) Abnormal chest radiography was significant finding with P. falciparum monoinfection.
5) P. falciparum monoinfection has emerged as single significant cause of cardiac morbidity in pediatric malaria patients. Morbidity though is severe, it is completely reversible on timely initiation of treatment. There was no mortality in the present study.

Limitations of Study:
1. Limited sample size
2. Area of coverage was limited

Future research is required to further delineate and characterize the prevalence, frequency, and cardiovascular morbidity in pediatric malaria patients.

Future prospect study should be developed in cooperating large sample size and mass study with appropriate methodology to capture the frequency and prevalence of cardiovascular morbidity in pediatric malaria patients.

Abbreviations:

ACT	:Artemisinin-based combination therapy
API	:Annual parasite index
ARDS	:Acute respiratory distress syndrome
ARF	:Acute renal failure
AL	:Artesunate plus Lumefantrine combination
AS	:Artesunate
AS+AQ	:Artesunate plus Amodiaquine combination
AS+MQ	:Artesunate plus Mefloquine combination
AS+SP	:Artesunate plus Sulfadoxine-Pyrimethamine combination
BUN	:Blood Urea Nitrogen
C	:Celcius
CBC	: Complete blood count
CK-MB	:Creatine kinase muscle-brain
ECG	:Electrocardiography
F	:Fahrenheit
GCS	:Glasgow Coma Scale
G6PD	:Glucose-6-phosphate dehydrogenase
Hb	:Hemoglobin
H-FABP	:Heart-type fatty acid-binding protein
HIV/AIDS	:Human immunodeficiency virus/acquired

immunodeficiency syndrome
HRP2 :Histidine-rich protein 2
ICT :Immune chromatographic test
IV :Intravenous
LFT : Liver function tests
LV :Left ventricle
MQ :Mefloquine
MR :Mitral regurgitation
NIMR :National Institute Malaria Research
NMEP :National Malaria Eradication Programme
NSAIDS :Non- steroidal Anti-Inflammatory Drugs
NT-pro BNP :N-terminal Pro-Brain Natriuretic Peptide
NVBDCP :National Vector Born Disease Control Programme
P :Plasmodium
PBS :Peripheral Blood Smear
PCR :Polymerase Chain Reaction
*Pf*HRP2 :Plasmodium Falciparum Histidine-rich Protein-2

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