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Cardiovascular involvement in severe vivax and falciparum malaria

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ABSTRACT

Background & objectives: Recently, vivax malaria is also presenting as severe malaria causing multiorgan dysfunction similar to falciparum malaria. The present study was undertaken to evaluate the involvement of cardiovascular system in severe malaria.

Methods: This is a clinical prospective study conducted on the cases of severe malaria in S.P. Medical College and PBM Hospital, Bikaner, India. In total, 100 cases (45 males, 55 females; age range 13–75 yr) of severe malaria (*P. vivax* 60; *P. falciparum* 28; and mixed 12) diagnosed by peripheral blood smear examination, rapid card test and PCR were studied. Evaluation of cardiovascular system was done by clinical examination, chest X-ray, ECG, high resolution transthoracic echocardiography and estimation of cardiac markers.

Results: In all, 17% cases (9 *P. falciparum*, 5 *P. vivax* and 3 mixed) were found to be suffering from cardiovascular involvement (11% circulatory failure, 7% congestive cardiac failure and 2% pulmonary edema). ECG showed sinus tachycardia in all the 17 patients, one had atrial ectopic and eight had non-specific ST-T changes. Cardiomegaly was seen in eight cases and pulmonary edema in two on X-ray chest. Echocardiography was within normal range but cardiac dimensions were increased in all the 17 cases. Troponin-I and CPK-MB were increased in 14 cases. Cardiovascular involvement in *P. falciparum* and mixed infection was associated with high parasite density but *P. vivax* infection was associated with relatively low parasite density. Involvement of cardiovascular system was associated with increased hospital stay (7.67 ± 2.23 *vs* 6.59 ± 0.87 days; $p < 0.001$) and high mortality (5 died out of 17 patients). Significant ECG changes and cardiac markers indicate myocardial involvement in severe malaria.

Interpretation & Conclusion: The present study indicates involvement of cardiovascular system in severe malaria as evidenced by changes in ECG and cardiac markers (Trop 1 and CPK-MB). The present study also highlights that vivax malaria is no more benign and pathophysiology of vivax malaria should be re-evaluated.

Key words Cardiac markers; circulatory failure; congestive cardiac failure; falciparum malaria; pulmonary edema; vivax malaria

INTRODUCTION

Cardiovascular manifestations in severe falciparum malaria include mainly hypotension, acute pulmonary edema, toxic myocarditis and conduction abnormalities[1–2]. There are also case reports on pericardial tamponade, endomyocardial fibrosis, peripheral gangrene, cardiomyopathy, shock and cardiac arrhythmias[3–11]. In addition to severe falciparum parasitemia and sequestration, secondary infections, severe anaemia, hypoxia, hyperpyrexia, dehydration/fluid overload, metabolic acidosis and disseminated intravascular coagulation can also contribute to the cardiovascular problems in malaria[7]. So far, only limited data and few case reports are available on myocardial involvement in falciparum malaria[11]. We have been observing severe manifestations also in vivax malaria, therefore, this prospective study was planned to evaluate cardiovascular manifestations in all types of severe malaria and to study the effect of these on associated morbidity and mortality.

MATERIAL & METHODS

This prospective study was conducted on patients of severe malaria who were admitted during July 2010 to June 2011 in the Department of Medicine, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, India. Informed consent was taken from patient or patient's relatives. Ethical clearance was obtained from the Institutional Ethics Committee, S.P. Medical College, Bikaner, India.

Inclusion criteria

Only those cases of severe malaria having the asexual forms of *Plasmodium* in the blood by smear examination were included in the study. The diagnosis of severe malaria was done as per WHO 2006 guidelines (Table 1)[12].

Exclusion criteria

Patients who refused to give the written consent or had other concurrent illness or pre-existing diseases like

Table 1. WHO criteria for severe malaria

Manifestation	Features
Cerebral malaria	Unrousable coma not attributable to any other cause, with a Glasgow Coma Scale score ≤9. Coma should persist at least for 30 min after a generalized convulsion
Severe anaemia	Hematocrit <15% or hemoglobin <50 g/l in the presence of parasite count >10,000/µl
Renal failure	Urine output <400 ml/24 h in adults (<12 ml/kg/24 h in children) and a serum creatinine >265 µmol/l (>3 mg/dl) despite adequate volume repletion
Pulmonary edema and acute respiratory distress syndrome	The acute lung injury score is calculated on the basis of radiographic densities, severity of hypoxemia, and positive end-expiratory pressure
Hypoglycemia	Whole blood glucose concentration <2.2 mmol/l (<40 mg/dl)
Circulatory collapse (algid malaria)	Systolic blood pressure <70 mmHg in patients >5 yr of age (< 50 mmHg in children aged 1–5 yr), with cold clammy skin or a core-skin temperature difference >10°C
Abnormal bleeding and/or disseminated intravascular coagulation	Spontaneous bleeding from gums, nose, gastrointestinal tract, or laboratory evidence of disseminated intravascular coagulation
Repeated generalized convulsions	≥3 convulsions observed within 24 h
Acidemia/acidosis	Arterial pH <7.25 or acidosis (plasma bicarbonate <15 mmol/l)
Macroscopic hemoglobinuria	Hemolysis not secondary to glucose-6-phosphate dehydrogenase deficiency
Impaired consciousness	Rousable mental condition
Prostration or weakness	
Hyperparasitemia	>5% parasitized erythrocytes or >250, 000 parasites/µl (in non-immune individuals)
Hyperpyrexia	Core body temperature >40°C
Hyperbilirubinemia	Total bilirubin >43 µmol/l (>2.5 mg/dl)

cardiac diseases, hypertension, diabetes mellitus, COPD, hepatitis B and C, typhoid fever, HIV, tuberculosis, etc. were not included in the study.

Diagnostic methods used to detect malaria parasite

The diagnosis of malaria was confirmed by gold standard method of peripheral blood smear examination of thick and thin smears by demonstration of asexual form of *Plasmodium*. The RDTs were based on detection of specific *Plasmodium* spp. Lactate dehydrogenase (OptiMal test; Diamed AG, Cressier sur Morat, Switzerland) and histidine rich protein 2 (Falcivax test; Zephyr Biomedical Systems, Goa, India). Evidence of *Plasmodium* spp was further confirmed by PCR. The PCR studies were targeted against the 18S ribosomal RNA gene of the parasite and used 1 genus-specific 5′ primer and 2 species-specific 3′ primers in the same reaction mixture.

All the patients were evaluated as per proforma (CRF). Assessment for cardiovascular involvement was done by: (a) Thorough clinical examination of cardiovascular system; (b) Chest X-ray: Looking for any evidence of cardiomegaly, lung field congestion; and (c) Standard 12-lead ECG: Following 14 points were analyzed carefully in every ECG: (1) standardization (calibration) and technical features (including lead placement and artifacts); (2) rhythm; (3) heart rate; (4) PR interval/AV conduction; (5) QRS interval; (6) QT/QTc interval; (7) mean QRS electrical axis; (8) P-waves; (9) QRS voltages; (10) precordial R-wave progression; (11) abnormal Q waves; (12) ST segments; (13) T-waves; and (14) U-waves. Serial tracings were recorded in all the patients till discharge.

Cardiac markers: Cardiac marker assay for Troponin–I and CPK–MB were done in all the patients who presented with severe malaria. Those patients who initially presented with increased serum level of these markers, were reevaluated after 21 days of follow up.

High-resolution transthoracic echocardiograms: A complete echocardiographic examination was performed with usual standard technique using 2.5 and 5.0 MHz transducers. Echocardiography was done in 95 patients, five patients who expired on the same day of admission could not be taken for echocardiography. The examination was performed with simultaneous registration of a reference ECG lead. Left parasternal, short axis, apical four-chamber and subcostal views were obtained for proper visualization of all four chambers, great vessels and pericardium. All measurements and calculations were based on M-mode tracings in three cardiac cycles as per recommendations of the American Society of Echo-cardiography. Following parameter were taken—left ventricular internal dimension-end systolic (LVESD) and end diastolic (LVEDD), interventricular septal thickness (end di-

astolic, DIVST), left ventricular post wall thickness (end diastolic, DLVPWT), left ventricular ejection fraction (EF%), peak velocity of early filling phase (Ei), peak velocity of atrial filling phase (Ai) and Ei/Ai ratio.

Other laboratory investigations: CBC including total leukocyte count (TLC), differential leukocyte count (DLC), hemoglobin (Hb), packed cell volume (PCV), platelet counts, blood glucose level, blood urea and serum creatinine, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, serum protein, albumin and globulin, and urine examination were done in all the cases. Dengue serology was also done to rule out dengue fever. Lumbar puncture and CSF analysis was done in all the doubtful cases to rule out other diseases like meningitis and encephalitis. Other relevant diagnostic tests were also done to rule out any other systemic or cardiac illness.

Statistical analysis: Statistical analysis was done using MS Excel and SPSS version 11. Data analysis of various parameters and their comparative statistical significance was evaluated by applying Chi-square (χ^2) test, *p*-value of <0.05 was taken as significant. Data analysis of parasite density was calculated by geometric mean.

RESULTS

A total of 642 cases of malaria (459 *P. vivax*, 147 *P. falciparum* and 36 mixed infections) during July 2010 to June 2011 were admitted in various wards of Department of Medicine, out of which 100 consecutive cases of severe malaria (45 males and 55 females; age range 13–75 yr), excluding patients with concurrent illness or pre-existing diseases, proved by peripheral blood smear examination, rapid card test and PCR were studied. Out of these 100 cases, 60 were *P. vivax* (*Pv*), 28 were *P. falciparum* (*Pf*) and 12 were mixed infections. Flow chart of the study patients is shown in Fig. 1. Manifestations of severe malaria were severe anaemia (Hb <5 g%) in 27% patients, followed by hepatitis in 24%, respiratory distress in 23%, cerebral malaria in 25%, hypoglycemia in 3%, acute renal failure in 11%, abnormal bleeding in 17%, circulatory failure in 11%, pulmonary edema in 2% and hemoglobinuria in 4% patients (Table 2).

Out of these 100 cases of severe malaria, 17 were found to be suffering from cardiovascular manifestations 11 from circulatory failure (6 *Pf*, 2 *Pv* & 3 mixed), seven from congestive heart failure (3 *Pf*, 3 *Pv* & 1 mixed), and two from pulmonary edema (1 *Pf*, 1 mixed). Cardiovascular involvement was more commonly found in *P. falciparum* malaria as compared to *P. vivax* or mixed malaria (χ^2=13.68; $p \leq 0.001$) (Table 3).

Table 2. Manifestations of severe malaria

Severe manifestations	No. of patients (n = 100)	Percentage
Severe anaemia	27 (*Pv*-16; *Pf*-8; *Pv*+*Pf*-3)	27
Hepatitis	24 (*Pv*-9; *Pf*-11; *Pv*+*Pf*-4)	24
Respiratory distress	21 (*Pv*-13; *Pf*-4; *Pv*+*Pf*-4)	21
Cerebral dysfunction	25 (*Pv*-11; *Pf*-13; *Pv*+*Pf*-1)	25
Hypoglycemia	3 (*Pf*-2; *Pv*+*Pf*-1)	3
Acute renal failure	11 (*Pv*-4; *Pf*-6; *Pv*+*Pf*-1)	11
Bleeding disorder	17 (*Pv*-8; *Pf*-4; *Pv*+*Pf*-5)	17
Circulatory failure	11 (*Pv*-2; *Pf*-8; *Pv*+*Pf*-3)	11
Pulmonary edema	2 (*Pf*-1; *Pv*+*Pf*-1)	2
Hemoglobinuria	4 (*Pv*-1; *Pf*-3)	4
Multiorgan failure	11 (*Pv*-2; *Pf*-8; *Pv*+*Pf*-3)	11

Pv—*P. vivax* malaria (n=60); *Pf*—*P. falciparum* malaria (n=28); *Pf*+*Pv*— Mixed malaria (n=12).

Most common finding in ECG was sinus tachycardia which was present in 25% cases of severe malaria (including 17 cases with cardiovascular involvement) on Day 1 and in 11% cases on Day 2, however, none of the patients had sinus tachycardia at the time of discharge. Nonspecific ST-T changes were observed in 8% patients at the time of admission, 2% cases on Day 2 while none at the time of discharge. One patient had atrial ectopics. None of the patients had any abnormality of QRS complex.

M-mode echocardiography showed mean left ventricular end diastolic diameter (LVEDD) of 4.04 ± 0.4 cm (ranging from 3–4.4 cm), left ventricular end systolic diameter (LVESD) of 2.55 ± 0.44 cm (ranging from 2–3 cm), mean interventricular septal thickness (end diastolic) was 0.52 ± 0.14 cm (ranging from 0.3–0.7 cm) and left ventricular post-wall thickness (end diastolic) of 0.46 ± 0.08 cm (ranging from 0.3–0.6 cm). Left ventricular ejection fraction was 56 ± 1.04% and ranged from 55–65%. Pulse wave doppler studies showed the mean peak velocity of early filling phase (Ei), mean peak velocity of atrial filling phase (Ai), and the mean Ei/Ai ratio were within normal limits in all the patients. Nine patients had mild

Table 3. Distribution of cardiovascular manifestations in severe malaria

Malaria type	Total cases of cardiovascular manifestation (n=17)	Circulatory failure (n=11)	Congestive heart failure (n=7)	Pulmonary edema (n=2)
Severe *P. falciparum* (n=60)	9	6	3	1
Severe *P. vivax* (n=28)	5	2	3	–
Severe mixed (n=12)	3	3	1	1

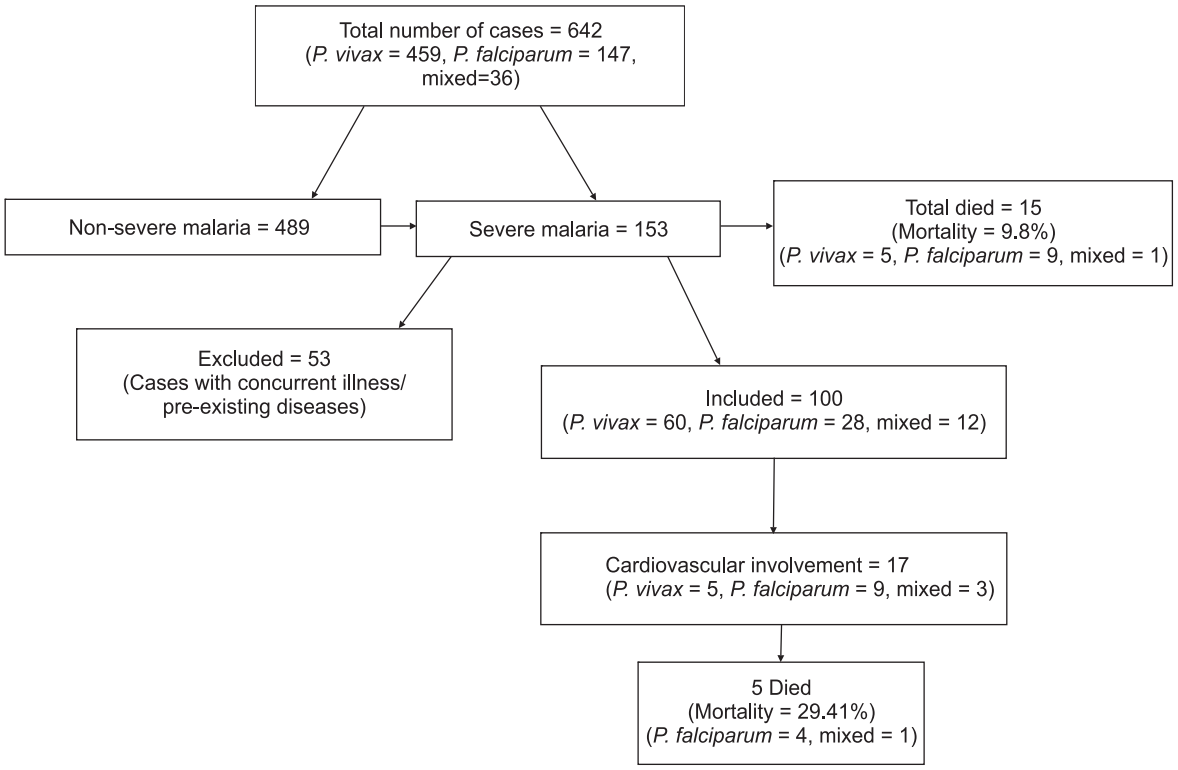

Fig. 1: Flow chart of the study patients.

mitral regurgitation, mild tricuspid regurgitation, mild aortic regurgitation and mild pulmonary regurgitation; these findings were present at the time of admission, on the day of discharge as well as on Day 21 of follow up. None of these patients had any valvular thickening. No patient had any evidence of pericardial effusion and regional or global hypokinesia. Although various echocardiographic parameters were within the limit of normal range but there was a significant difference between patients with or without cardiovascular involvement (Table 4).

Cardiac markers, both Troponin-I and CPK-MB were increased in 14% cases and were found normal in 3 out of 17 patients who presented with cardiovascular involvement (Table 5). Out of 17 patients, 11 of them developed circulatory failure presented with tachycardia, tachypnoea, decreased urine output, feeble pulses and hypotension. Multiorgan failure was present in all cases. X-ray chest showed cardiomegaly and bilateral basal lung infiltrate in two cases. ECG showed sinus tachycardia in all and non-specific ST-T changes in four cases. Echocardiography did not show any significant valvular thickening, four patients showed mild regurgitant lesions at the time of admission which persisted even after 21 days of follow up. Circulatory failure was found more commonly in severe falciparum infection than vivax or

Table 4. Echocardiographic parameters in severe malaria

Echocardiographic parameter (mean ± SD)	With cardiac involvement (n = 17)	Without cardiac involvement (n = 83)	χ^2	*p*-value
LVEDD (cm)	4.04 ± 0.4	3.76 ± 0.43	3.84	0.0001
LVESD (cm)	2.55 ± 0.44	2.45 ± 0.34	5.18	0.0001
DIVST (cm)	0.52 ± 0.14	0.53 ± 0.10	1.48	0.5
DLVPWT (cm)	0.46 ± 0.08	0.49 ± 0.09	2.66	0.01
EF (%)	56.34 ± 1.04	59.11 ± 1.12	2.82	0.01

Table 5. Cardiac markers in patients of severe malaria with cardiovascular system involvement (n = 17)

Patients S.No.	1	2	4	11	18	21	22	26	32	34	40	56	60	63	68	88	90
Type of malaria	*Pv*	M	*Pf*	*Pv*	*Pf*	M	*Pv*	*Pf*	M	*Pf*	*Pf*	*Pv*	*Pv*	*Pf*	*Pf*	*Pf*	*Pf*
Trop-I (µg/l)	1.1	1.5	0.9	1.23	<0.01	1.96	<0.01	1.45	1.23	2.1	1.73	1.89	<0.01	0.78	1.39	1.95	1.63
CPK-MB(IU/dl)	6.2	7.4	5.9	6.7	0	9	0	6.2	7.3	9.4	8.1	6.5	0	7.7	8.4	9.2	8.9

Pv— *P. vivax* malaria; *Pf*— *P. falciparum* malaria; M— Mixed malaria.

mixed infection. Out of total 11 patients of circulatory failure, five patients expired (mortality = 45.45%).

Congestive heart failure was observed in seven cases. All of them had Hb ≤5 g% and presented with dyspnoea, lethargy, pallor, tachypnoea, tachycardia, a gallop rhythm and tender hepatomegaly. These patients were treated with diuretics and slow correction of anaemia by packed cell transfusion. All the patients recovered except one who was in circulatory failure. Cardiomegaly was found in all the patients with congestive heart failure. ECG showed sinus tachycardia in all and non-specific ST-T changes were found in four patients. Echocardiography showed increased cardiac dimension with normal systolic and diastolic functions.

Two cases had pulmonary edema presented with dyspnoea, tachypnea, hypotension, bilateral coarse crepts and decreased urine output. Both patients had multiorgan dysfunction. Chest X-ray showed increased vascular marking including thickening of the interlobular septa and bilateral lung infiltrate. ECG showed sinus tachycardia in both patients. Echocardiography did not show any significant valvular lesion although one patient had mild MR, TR and AR at admission.

The parasite density (PD) was higher in patients with cardiovascular involvement (geometric mean PD = 14563.68/µl) than those without cardiovascular involvement (geometric mean PD = 8190.65/µl). In patients with cardiovascular involvement, parasite density was highest in those who were suffering from *P. falciparum* infection (geometric mean PD = 27439.95/µl) followed by mixed malaria (geometric mean PD = 21253.17/µl) while in *P. vivax* malaria geometric mean parasite density was 3711.74/µl ($p \leq 0.001$). This shows that severe malaria (including with cardiovascular involvement) due to *P. vivax* infection was associated with relatively lower parasite density (Table 6).

Cardiovascular manifestations were associated with high mortality rate. Case fatality rate in circulatory failure was 45.45%, in pulmonary edema was 100%, and in congestive heart failure was 14%. Other prognostic indicators were multi-organ failure, severe anaemia, acute renal failure and respiratory distress (Table 7).

Table 7. Severe manifestations and associated mortality in severe malaria

Severe manifestations	Prevalence (n=100)	Mortality No. (%)	χ^2	*p*-value
Severe anaemia	27	3 (11.11)	13.68	0.0002
Cerebral dysfunction	25	4 (16)	5.82	0.015
Hepatitis	24	5 (20.83)	13.07	0.0003
Acute renal failure	11	5 (45.45)	1.7	0.192
Respiratory distress	21	5 (23.80)	24.97	0.0001
Circulatory failure	11	5 (45.45)	13.89	0.0001
MODS	11	5 (45.45)	34.58	0.0001
Pulmonary edema	2	2 (100)	–	–

DISCUSSION

Reports on cardiovascular manifestations in malaria are very few and most of them are case reports in falciparum malaria[1–11]. Present study was conducted to see the prevalence and type of cardiovascular manifestations in severe malaria using 12 lead ECG monitoring, radiological chest examination, cardiac markers and high-resolution transthoracic echocardiogram.

The present study showed cardiovascular manifestations in 17% of the cases and 11% had circulatory failure. Myocardial function is generally well-preserved in severe falciparum malaria[9, 13–14]. The cardiac index may be elevated with low peripheral vascular resistance and low to normal ventricular filling pressures. Hypovolumia (due to reduced fluid intake, high grade fever, sweating, vomiting and diarrhoea) also may contribute to the reduced pressures. Orthostatic hypotension is common. Septicemia, metabolic acidosis and hypoxia may result in a drop in cardiac index[15]. The pathophysiology of myocardial injury in falciparum malaria remains obscure. Ischemia, acidosis, toxic effects of substances like falciparum glycosyl-phosphatidyl-inositol, or *Plasmodium*-triggered mechanisms like apoptosis may be responsible for myocardial damage[7, 9]. In our study, patients with circulatory failure presented with tachycardia, tachypnoea, decreased urine output, feeble pulses and hypotension, patients who died had a greater number of these signs than survivors. These patients had history of vomiting in

Table 6. Parasite density in severe malaria patients (n = 100) (with and without cardiovascular involvement)

	Cardiovascular involvement (n = 17)				No cardiovascular involvement (n = 83)			
Type of malaria	*P. falciparum*	*P. vivax*	Mixed	Total	*P. falciparum*	*P. vivax*	Mixed	Total
No. of cases	9	5	3	17	19	55	9	83
Range of parasite density	1800–56000	800–8600	8000–40000	800–56000	2000–40000	400–40000	1200–28000	400–40000
Geometric mean	27439.95	3711.74	21253.17	14563.68	9190.03	5885.70	4802.91	8190.65

46%, and abnormal bleeding in 13% (epistaxis in 12%, and hemetemesis in one case). High grade fever, excessive sweating and inadequate fluid intake may also have contributed to dehydration seen in some patients. Multiorgan failure was present in all the cases of circulatory failure, with anaemia in all the cases (severe anaemia in 4; moderate anaemia in 5; and mild anaemia in 2 patients), hepatitis in 8 (72.72%), renal failure in 8 (72.72%), cerebral dysfunction in 5 (45.45%), respiratory distress in 8 (72.72%), and pulmonary edema in 2 (18.18%) cases suggesting multiorgan pathogenesis of circulatory failure. Myocarditis may have a role in circulatory failure seen in our cases as shown by raised cardiac markers[13].

Mortality with circulatory failure (45.45% in our study) was higher that was similar to other studies, the majority of patients with circulatory collapse died within 24–48 h after admission emphasizing the need for triage and early treatment[6, 8].

The present study showed congestive heart failure in seven cases, all of them had Hb ≤5 g% and cardiomegaly. Although cardiac enlargement is usually seen in chronic anaemia, but, if it is present in acute anaemia it is a result of presence of other cardiovascular disease, may be acute malarial myocarditis in our patients[16].

We observed two cases of pulmonary edema. Both patients had multi-organ dysfunction such as anaemia, respiratory distress, renal failure and cerebral dysfunction and both of them died (mortality 100%). Acute pulmonary edema is a grave and usually fatal complication of severe falciparum malaria with >50% mortality. Pulmonary edema develops later compared to other complications and it may even appear several days after treatment for malaria, when the patient is otherwise improving with a reduction in peripheral parasitaemia. The mechanism of pulmonary edema is not clearly understood. It has a close resemblance to adult respiratory distress syndrome. While over-hydration may be the cause in some cases of pulmonary edema, it can also develop in patients with normal capillary wedge pressures. Such cases may be due to increased permeability of pulmonary capillaries, sequestration of red cells and clogging of pulmonary microcirculation and disseminated intravascular coagulation[5]. Pulmonary edema is more common in patients with hyperparasitaemia, renal failure and it is commonly associated with hypoglycemia and metabolic acidosis.

All the patients with cardiovascular involvement who revealed mild regurgitant lesions were mild to severely anemic. Similar valvular lesions were also present in five patients of severe malaria in whom no other abnormality of cardiovascular system was found but they were having severe anaemia. Repeat 2D-ECHO after 21 days follow up in such patients showed similar findings. As we did not find any abnormality of anatomy of valvular cusps, regurgitant lesions can be explained by anaemia present in such cases, although possibility of malarial cause can not be ruled out, large-scale study and long-term follow up of such patients may be required.

ECG changes seen in our study may indicate early myocardium involvement because electrophysiology of cardiac myocytes alters before changes could be seen on echocardiography. Although it can also be explained by the presence of severe anaemia, these changes can also be due to a variety of other factors like hyperventilation, anxiety, body position, food, neurogenic influences, temperature, electrolyte imbalance, allergic reactions. Similarly, previous studies have shown a variety of abnormality on ECG but these bear uncertain correlation with clinical and functional status of heart[17].

Mohapatra *et al*[18] showed involvement of the myocardium in cerebral malaria, it can cause myocardial injury, reversible global hypokinesia similar to myocardial stunning and diffuse myocardial necrosis as evidenced by raised Troponin-T, echo, and autopsy.

Thus, our study concludes that there is involvement of cardiovascular system in severe malaria as shown by changes in ECG and cardiac markers (Trop. I and CPK-MB) indicating myocardial involvement and it is associated with increased morbidity and mortality. Limitations of our study were that: (i) we could not do immediate bed side echocardiography as this facility was not available, patients had to be shifted to echo-room for the investigation; and (ii) we did only 21 days follow up. Further studies including bed side echocardiography, Holter monitoring and long-term follow up may put more insight on cardiovascular system involvement in malaria. Our study also showed that severe vivax malaria (including with cardiovascular involvement) is associated with relatively lower parasite density as compared to falciparum and mixed infection. This has been first reported by us and it shows that vivax malaria is no more benign and pathophysiology of vivax malaria should be re-evaluated.

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