The Natural History of Complicated Falciparum Malaria — A Prospective Study

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Abstract

Objective: Despite a substantial disease burden, little is known about the natural history of complicated falciparum malaria. Therefore, the present prospective study was undertaken to assess the clinical course, outcome, and resolution time of various complications of falciparum malaria.

Methods: This prospective study has been conducted in a tertiary health care institution with high prevalence of malaria. A cohort of 608 patients of complicated falciparum malaria with single and multiple complications were enrolled. After discharge, all patients were followed up for 1 month except patients with anaemia who were followed up for 3 months. The onset time, interval of progression of one complication to other, resolution time of complications and mortality were determined.

Results: At the time of admission there were 288 (46.8%) patients with single complication (SC) and 320 (53.2%) patients with multiple complications (MC). Majority (n=214, 74.3%) of patients with SC had cerebral malaria, followed by jaundice (14.6%), anaemia (6.9%), hypoglycaemia (2.1%), and respiratory distress (2.1%). The multiple complications were found in various combinations and majority (n=136, 42.5%) had constellation of 3 different complications. Cerebral malaria, jaundice, and renal failure (102 of 136, 75.3%) were the most common combination. Regardless of number of complications, cerebral malaria was present in 91.6% (293 of 320) patients with MC. As the population of patients progressed from single to multiple complications, increasing proportions had jaundice, renal failure, and anaemia. 12.8% to 36.2% of patients in any category progressed from one complication to other complication within 72 hrs. There mortality rate was 14.6%, 21.3%, 30.9%, 38.5%, 100%, and 100% among patients with 1, 2, 3, 4, 5, and 6 complications respectively.

Conclusion: This is the first prospective study that provides the clinical evidence that complicated malaria represents a hierarchical continuum of abnormalities resulting from falciparum infection. All complications developed within 5 days (median 72 hrs, range-2 to120hrs.) of onset of fever. Pre-pernicious stage had been recognised in cases of cerebral malaria. Each complication is unique in its onset and recovery time. Not only the number but also the type of complication influences the outcome of complicated malaria. ©

INTRODUCTION

Malaria still remains, today as it has been for centuries; one of the most serious parasitic disease of the world affecting 300-500 million people and causing over 1 million deaths each year.1 Of the four species of plasmodia causing human malaria, P. falciparum has the potential for developing life threatening complications, which may result in fatality. Cerebral malaria is the commonest form of complicated falciparum malaria encountered in clinical practice. However, presently a large spectrum of clinical conditions is summarised under the term complicated malaria.2 Not surprisingly, in fatal cases malaria may be complicated with multiple organ dysfunction, the cumulative effects of which causes fatality.3

Inspite of considerable progress in understanding the pathogenesis of the disease, the treatment mortality rate of cerebral malaria is 15-22 % and it can rise above 30% when associated with multiple organ dysfunction.4,5 As a large spectrum of clinical conditions has been included under complicated malaria, understanding the onset, duration, resolution, and outcome of various complications assume paramount importance. As a result, timely intervention may prevent the progression; hence reduce the mortality. Therefore, this prospective study has been undertaken to analyze the natural history of various forms of complicated malaria.

MATERIAL AND METHODS

This study was a single centre prospective study on complicated malaria conducted at M.K.C.G. Medical
College and Hospital, Berhampur, Orissa. Consecutive adult patients of smear positive falciparum malaria with various complications admitted to Department of Medicine from January 1996 to December 2002 were included in this study. As the coexistence of other diseases may influence the outcome of complicated malaria, patients with diseases like diabetes mellitus, chronic renal failure, chronic liver disease, rheumatic heart disease, coronary artery disease, and associated infections like pneumonia, urinary tract infection and viral hepatitis were excluded. Cerebrospinal fluid analysis, abdominal ultrasound, chest X-ray, and serological markers for viral hepatitis were done to exclude these diseases.

The diagnosis of malaria was made with detection of asexual form of P. falciparum from Giemsa stained peripheral blood smear. Severe malaria was diagnosed according to the guidelines of World Health Organization. Cerebral malaria was diagnosed when a patient had unarousable coma using Glasgow Coma Scale with exclusion of other encephalopathies. Renal failure, jaundice, hypoglycaemia, and severe anaemia were diagnosed when s. creatinine was more than 2.0 mg/dl, s. bilirubin was more than 2.0 mg/dl., random blood glucose was less than 60 mg/dl, and haemoglobin was less than 7.0 gm/dl respectively. Circulatory collapse (hypotension) had been defined as systolic blood pressure (BP) < 90 or a fall in BP of more than 40 mm of Hg unresponsive to fluid administration. Respiratory distress was defined when patient had tachypnoea with or without pulmonary oedema.

On admission, peripheral blood smears were collected for Giemsa staining on admission and subsequently every 12 hours to assess parasitemia. Blood was collected for estimation of glucose, urea, creatinine, sodium, albumin, bilirubin, aspartate amino transferase, alanine amino transferase, and for haematological investigations such as haemoglobin, platelet count, total leukocyte count, and prothrombin time (PT). All the investigations except platelet count and PT were continually scaled to assess the progression and recovery of various complications of the disease. The pH, pCO$_2$ and pO$_2$ were gauged and chest x-ray was done in 26 cases for diagnosis of respiratory distress (RD) and pulmonary oedema.

Patients with one complication were grouped under single complication (SC) and with 2 or more complications under multiple complications (MC). Onset time, resolution time, duration, and progression of complications as well as duration of hospital stay were determined. Assuming fever as the onset of clinical malaria, the interval of fever to the onset of various complications has been defined as the onset time of the respective complications. Thus onset time of coma, renal failure, anaemia, hypoglycaemia, jaundice, respiratory distress, and hypotension were determined. Recovery time of individual complication, parasitic clearance time, and fever clearance time were calculated from the initiation of treatment. Among the patients with MC, time taken from one complication to develop another was determined from onset time of various complications. Average duration of complication had been calculated from the time of onset of individual complication to full recovery of the respective complication.

The outcome was binary i.e. either recovery or death. Patients were examined and assessed twice daily until full recovery or death. All patients were followed up for 1 month and patients with anaemia were followed up for 3 months after discharge.

All patients were treated with intravenous quinine dihydrochloride at a loading dose of 20mg/kg administered over 3 hrs. Subsequent dose of 10 mg/kg administered over 2 hrs every 8 hrs in a 10% dextrose solution until the patient could take medication orally. Treatment was continued for 7 to 10 days. Complications such as anaemia, hypoglycaemia, convulsion, renal failure, jaundice, and circulatory collapse were treated appropriately.

SPSS (Version-10) software was used for all statistical calculations. Patient characteristics and the outcome of interest and relative risk and their corresponding 95% confidence interval were calculated. For continuous variable, mean values were compared using two sample t tests for independent samples. Mean values are reported ± 1 SD. The trends in mortality were examined with X$^2$ statistics for linear trends. The probability ≤ 0.05 was considered as significant. Kaplan-Meier survival curve was calculated for time to death in patients with SC and MC.

**RESULTS**

A cohort of 608 patients of complicated falciparum malaria was enrolled in this study. Most patients (n=408, 67.1%) were younger than 40 years of age, and the male-to-female ratio was 1.9:1 (400:208). There were 208 (34.2%) females, a quarter (n=52) of whom were pregnant. The mean weight of male patients was 46.8±11.2 and female patient was 41.6±12.4 Kg.

There were 288 (46.8%) patients with single complication (SC) and 320 (53.2%) patients with multiple complications (MC). Of 288 patients with SC, cerebral malaria, jaundice, anaemia, hypoglycaemia, and RD constituted 74.3%, 14.6%, 6.9%, 2.1%, 2.1% patients respectively. Of 320 patients with MC, 42.5%, 30.4%, 24.4%, 2.5%, 1.3% patients had a constellation of 3, 2, 4, 5, and 6 different types of complications respectively (Table 1). The multiple complications were found in various combinations, of which constellation of cerebral malaria, jaundice, and renal failure was common (102 of 136, 75.3%). Cerebral malaria was present in 91.6% (293 of 320) patients with MC. Only 27 (8.4%) patients had non-cerebral multiple complications. Multiple complications
were more (61.5%, 32 of 52) in patients with pregnancy compared to their non-pregnant counterpart (51.9%, 108 of 208 p<0.05).

Onset time of various complications

(a) Single complication: The coma onset time ranged from 2 hours (hrs) to 5 days with a mean interval of 54.7±34.0 hrs (med. 48, 95%CI=50.2 to 59.2). Forty (18.7%) patients developed coma within 12 hrs. and 84 (39.3%) patients within 24 hrs of onset of fever. The mean onset time (median with 95% confidence interval) for hypoglycaemia, RD, jaundice, and anaemia was 9.7±2.3 (med. 12, 95%CI=7.9 to 11.5), 13.0±7.0 (med. 14, 95%CI=9.0 to 17.0), 68.8±30.3 (med. 72, 95%CI=59.6 to 77.9), and 108.5±21.9 (med. 108, 95%CI=98.9 to 118.1) hrs respectively.

(b) Multiple complications: In 45 (14.1%) patients, multiple complications developed within 24 hrs of onset of fever, where as in rest 275 (85.9%) cases it developed sequentially with development of one complication after another. The mean onset time (median with 95% confidence interval) of hypotension, respiratory distress, coma, jaundice, renal failure, and anaemia was 11.5±4.8 (med. 12, 95%CI=6.8 to 16.2), 13.9±4.8 (med. 12, 95%CI=11.9 to 15.9), 54.7±42.1 (med. 48, 95%CI=49.9 to 59.5), 80.9±46.9 (med. 72, 95%CI=75.3 to 86.5), 94.5±32.2 (med. 96, 95%CI=90.3 to 98.7), and 106.2±21.5 (med. 108, 95%CI=102.8 to 109.6) hrs respectively (Fig. 1). Comparison of mean onset time of complications found as SC and as a component of MC did not show any statistical significance (p>0.1).

Pre-pernicious stage

Pre-pernicious stage had been recognised in cases of cerebral malaria. Before onset of deep coma, 45.2% patients of cerebral malaria from both groups of SC (104 of 214, 47.7%) and MC (125 of 293, 42.6%) had a pre-comatose period ranging from 5 to 24 hrs (mean 18.9±8.7 hrs.). This period is characterised by disorientation, severe headache, and transient loss of consciousness, nightlong insomnia, and incontinence of urine without loss of consciousness. In other complications pre-pernicious symptoms could not be detected.

Progression, duration, and resolution of complications

110 (36.2%) patients of SC progressed to MC within...
6 to 96 hrs (mean 44.5 ± 25.6, med.45 hrs. 95%CI-39.8 to 49.2) in the hospital. Of them, 46 (41.8%) and 64 (58.2%) patients progressed within 24 (13.4 ± 6.3) and 72 (53.2 ± 21.9) hrs of hospitalisation. Among patients with MC, 23.4% (22 of 94) patients with 2, 27.9% (38 of 136) with 3, and 12.8% (10 of 78) with 4 complications progressed to next higher complication within 72 (54.5±12.4) hrs. Of them 25.7% (18 of 70) progressed within 24 (12.8 ± 4.6) hrs.

The mean parasite clearance time and fever resolution time was 48.2 ± 25.6 hrs (med.50, 95%CI-46.2 to 50.3) and 47.8 ± 24.8 hrs (med.48, 95%CI-46.2 to 50.2). The mean recovery time (median with 95%CI) of hypoglycaemia, coma, jaundice, renal failure, hypotension, RD, and anaemia was 1.8±0.3 hrs (med. 2, 95%CI-1.5 to 2.1), 95.5 ± 35.2 hrs (med.120, 95%CI-80.6 to 121.7), 248.8±36.7 hrs (med.240, 95%CI-214.3 to 224.8), and 56.6 ± 24.8 days (med.60, 95%CI-50.9 to 62.0) respectively. Each complication has a different resolution time, which was almost same whether the complication was present as SC or as a part of MC.

The average duration of hypoglycaemia, hypotension, coma, jaundice, RD, renal failure, and anaemia were 12.6±6.8 hrs (med.8, 95%CI-10.2 to 15.0), 28.6±11.2 hrs (24, 95%CI-17.7 to 39.5), 82.4±21.6 hrs (med.85, 95%CI-80.6 to 84.2), 180.5±32.8 hrs (med.184, 95%CI-176.9 to 184.2), 192.2±56.8 hrs (med.182.9, 95%CI-182.9 to 201.4), 221.8±56.8 hrs (med.224, 95%CI-214.3 to 229.3), and 57.8 ± 28.9 days (med.60, 95%CI-53.6 to 62.0) respectively.

Parasitic count and complications
It has been observed that the mean parasitic count was higher (9867.9 ± 789.7 / mm³) in patients with SC than patients (5798.8 ± 542.6 / mm³) with MC (p<0.02). In the former, the patients with hypoglycaemia had highest (8786.9 ± 239.5 / mm³) and anaemia had the lowest (3895.3 ±321.7 / mm³, P<0.01) parasitic count. The count for patients with cerebral malaria, jaundice, and RD was 6754.8 ±342.1 / mm³, 5432.8 ±145.8 / mm³, and 4387.9 ±231.8 / mm³ respectively. Patients with 5 or 6 complications had less number of parasites (1200.8 ±120.5 / mm³) in peripheral smear than patients with 2 complications (4586.3 ± 231.4 / mm³, p<0.01). Patients with 3 and 4 complications had the count of 3876.7±118.6 / mm³ and 3246.4 ± 135.8 / mm³.

Complications and mortality
The mortality rate of patients with SC and MC was 14.6% and 32.5% (p<0.01). The overall mortality was 24.0%. There is a significant linear increase in the percentage of mortality and number of complications. The mortality was 14.6%, 21.3%, 30.9%, 38.5%, 100%, and 100% for 1, 2, 3, 4, 5, and 6 complications respectively. (X² = 13.14, df = 5, p < 0.05). A Kaplan-Meier survival analysis showed that the mean (±SE) survival time was 6.6 (±0.8) days (Fig. 3). Out of 42 (20.2%) female deaths, death was more among pregnant women (26.9%) than non-pregnant women (17.9%, p <0.05).

Among patients with SC, mortality was 66.6% in patients with RD and 17.8% in cerebral malaria. However, there was no death in patients with jaundice, anaemia, and hypoglycaemia. Among patients with MC the mortality was high when combination of jaundice and renal failure was present (Table 1).

**DISCUSSION**

The results of this present study are notable for 3 reasons. First, they demonstrate that increasing number of patients has been complicated with multiple complications which developed sequentially one after
another or fulminantly within hours of development of fever. Second, each complication is different from other complication as regards to its onset time, recovery time, and fatality. Third, cerebral malaria has been preceded by a pre-pernicious stage.

In the last decade the clinical pattern of severe malaria has been changed in different parts of the world including India. In the changing scenario, the combination of jaundice and renal failure are more common than cerebral malaria alone. The present study shows that cerebral malaria alone or in combination with other complications is still the commonest form of complicated malaria. The constellation of 3 complications i.e. cerebral malaria, jaundice, and renal failure is more common than any other combination.

All complications developed within 5 days of onset of fever. 12.8% to 36.2% of patients in any category progressed from one complication to other complication within 72 hrs. One complication may progress to another sequentially or fulminantly skipping the time gap. Cerebral malaria, hypoglycaemia, pulmonary, and circulatory collapse are the complications that occur early (within 48 hrs), whereas jaundice, anaemia, and renal failure develop later (48 to 120 hrs). Clinical recognition of the pre-pernicious stage in cerebral malaria is important because intervention at this stage can prevent the progression to complicated malaria hence mortality.

The recovery sequence reveals that parasite clearance and abatement of fever occurred earlier than resolution of individual complication. Recovery of hypoglycaemia, coma, and circulatory collapse is earlier than recovery of other complications. Anaemia took more than a month to recover. Haemolysis of pRBC, reduced life span of non parasitized RBC, depression of bone marrow are the probable mechanisms for prolonged recovery. It is notable that the average time of onset and reversal of each complication is remarkably similar whether it presents as SC or as a component of MC. Recovery pattern showed that parasitic clearance did not affect the organ recovery. Due to sequestration of parasites in internal organs, patients with MC may have low parasitic count. Among the patients with SC, highest and lowest parasite count has been detected in hypoglycaemia and anaemia. Haemolysis and sequestration of pRBC may be the cause of low peripheral parasitic count in anaemia.

The mortality increased with increasing number of complications. The mortality was 14.6% among patients with SC and 100% among patients with 5 or 6 complications. Each new complication adds roughly 10-20% to the base line risk of death. In view of mortality, cerebral malaria and RD are considered to be most severe, while anaemia, jaundice, and hypoglycaemia are less severe form of complication. The combination of hypotension, respiratory (RD), renal failure, with cerebral malaria is found more fatal than combination of jaundice and anaemia. Hence, not only the number but also the type of complication influenced the outcome of complicated malaria which is similar to sepsis with multiple organ dysfunctions.

Several observations from the study of experimental as well as human cerebral malaria showed that at the cellular level various proinflammatory cytokines and several adhesion molecules play important roles in the pathogenesis of complicated malaria, which is strikingly similar to sepsis. Sequestration of pRBC restricts local blood flow to various organs and subsequently damages the endothelial cell that results in generalized circulatory changes, manifesting as pulmonary oedema, acute renal failure, liver damage, and severe hypotension. Therefore once the complications develop removal of parasites could not reverse the organ damage and hence the mortality. Hence, in addition to antimalarial drugs, organ support is mandatory in the management of severe malaria. In summary, the present study describes the natural history of complications of complicated falciparum malaria in a large cohort of patients. The knowledge of natural history will help in early diagnosis and prompt treatment, which is crucial for reducing mortality.

REFERENCES


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**Announcement**

First Annual Conference of Indian Society of Cardiology, 10th-12th November 2006 at Udaipur, Rajasthan, India. Organized by: R.N.T. Medical College, Udaipur (Rajasthan).

Prof. SK Kaushik, Organizing Secretary, Head, Department of Cardiology, R.N.T. Medical College, Udaipur.

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