Original Article

Jaundice in Falciparum Malaria; changing trends in clinical presentation — a need for awareness

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Abstract

Objectives: To describe the clinical characteristics, laboratory parameters and prognostic factors in patients with falciparum malaria (FM) with jaundice.

Methods: A cross-sectional comparative study was conducted at the Department of Medicine, medical unit II, Jinnah Postgraduate Medical Centre, Karachi. Adult patients with jaundice and smear positive plasmodium falciparum infection, who fulfilled the inclusion criteria were selected for the study from amongst all cases of FM who presented during the study period. Patients were divided in to two groups on the basis of rising bilirubin and adverse outcome. The data was analyzed on SPSS ver 12. Results were expressed as, percentages, mean and standard deviations. P-value <0.05 was taken as significant.

Results: Among 76 patients of FM, 35(46.05%) developed jaundice. Fifteen (42.86%) patients had bilirubin 3-10mg/dl while 20(57.14%) had bilirubin >10mg/dl. Comparative analysis of the groups showed that elevation of ALT and AST was modest in comparison with conjugated hyperbilirubinaemia while prolonged duration of illnes impaired consciousness, hepatomegaly, acute renal failure with deranged renal parameters, low platelet counts and high parasite density were significantly associated with rising bilirubin and adverse outcome. Twenty-one (60%) patients recovered completely while 14(40%) succumbed to the disease.

Conclusion: FM is one of the causes of severe jaundice in adults in this part of the world. This presentation of complicated FM needs to be recognized globally in order to institute prompt and specific therapy. Delayed diagnosis and inappropriate treatment is the leading cause of complications and increased mortality in FM (JPMA 58:616; 2008).

Introduction

The global malaria situation is intensifying. Over two billion people now reside in areas where plasmodium falciparum (PF) is transmitted and each year 300-500 million new infections with this parasite result in 1.5-2.7 million deaths.[1] Each year 25-30 million people from non-tropical countries visit areas in which malaria is endemic, of whom between 10,000 and 30,000-contract malaria.[2]

In recent years, the clinical pattern of severe malaria has changed. Over a decade ago cerebral malaria was the predominant feature of severe malaria.[3] Cases of severe falciparum hepatitis and malarial acute renal failure were few and far between. Whereas today hepatic and renal involvement is seen more frequently and their mode of presentation has undergone a change, posing a diagnostic dilemma with other ailments particularly acute viral hepatitis or fulminanat hepatic failure, especially in endemic areas.[3,4]

Presence of jaundice in FM indicates a more severe illness with higher incidence of complications and poor prognosis.[5] The disease is more commonly seen in adults and in those areas of the tropics where transmission of malaria is low or unstable, especially in Asian countries, and where symptomatic disease occurs at all ages.[6] Jaundice in severe malaria is multi-factorial and can result from haemolysis of parasitized and non-parasitized red blood cells, hepatic dysfunction and possibly an element of microangiopathic haemolysis associated with disseminated intravascular coagulation (DIC).[3] It may be present alone or with other complications of FM and may vary from mild to very severe.[7]

Awareness of this entity is important not only in endemic areas, but also for non-endemic areas, as easy global travel allows severe imported FM to reach any part of the world.[2]

We have previously reported severe jaundice in association with FM, masquerading as fulminant hepatic failure.[8]

Over the years there has been a rise in the incidence and severity of jaundice in patients diagnosed as FM. The present study was conducted with the objective to describe clinical characteristics, biochemical parameters and prognostic factors in patients of FM with jaundice.

Patients and Methods

This open prospective case series study was conducted in the Department of Medicine, Jinnah Postgraduate Medical Centre, Karachi Pakistan over a

period of 2.5 years between May 2003 and November 2005. Jinnah Postgraduate Medical Centre is a1200 bed teaching hospital in Karachi and serves as a major tertiary care public-sector hospital, predominantly for urban underprivileged population. The study site is one of the three Medical Units in the Department of Medicine with 53 in-patient beds. It receives patients every third day.

This study was undertaken prospectively on consecutive patients presenting with clinical jaundice and confirmed to have FM by demonstration of asexual forms of PF in the peripheral smear.It included adult patients of both sexes and different ages after obtaining the formal consent from the patients or relatives. Thirty five such patients were enlisted during 2.5 years. Patients who had negative peripheral smear for PF, or had mixed plasmodium infection, and those who had evidence of any other disease or condition leading to jaundice or affecting the outcome of FM with jaundice, were excluded. Jaundice was defined as an icteric sclera and or total bilirubin levels >3mg/dl (50µmol/L). World Health Organization (WHO) criteria were used to describe the systemic complications.[5]

We evaluated all these patients for history of fever, duration of their disease, headache, and altered sensorium, vomiting, urinary output, renal failure, convulsions, pallor, icterus, hepatosplenomegaly and coma. Details of history and clinical assessment were noted in all patients on a pre-tested questionnaire. Other causes of liver dysfunction were excluded by appropriate investigations. All patients underwent a set of investigations such as a complete blood count and peripheral blood film (thick &thin) for the diagnosis of malaria and parasite count. Blood sugar, ECG and x-ray chest were done in all patients. Liver function was evaluated by determining the levels of total serum bilirubin, conjugated and uncojugated bilirubin, ALT, AST, alkaline phosphate, total proteins, serum albumin and prothrombin time. Blood tests for markers of hepatitis B and C were done in all patients to rule out any possibility of concomitant viral hepatitis. Renal profile included complete urine examination, urea, and creatinine and electrolytes. Ultrasonography was done to check the size and echo-texure of the liver, intra-hepatic, or extra-hepatic bile duct dilatation and signs of portal hypertension in all patients. Partial activated thromboplastin time and D-dimer were analyzed based on clinical suspicion of coagulopathy. Arterial blood gases, bleeding time, cerebrospinal fluid examination and blood cultures were done when indicated.

All patients received specific treatment in the form of intravenous quinine or intramuscular artemether using the standard regimen.[5] Whereas specific complications were treated according to the World Health Organization (WHO) protocol.[5] All patients were followed in hospital till death or recovery. The factors responsible for adverse outcome were noted in individual patients.

Data Analysis

To asses whether high or rising bilirubin was associated with derangement of other parameters, patients were classified in two groups. Group A bilirubin between 3-10 mg/dl and group B> 10mg/dl. Moreover, factors affecting the outcome were noted in individual patients. To asses the factors adversely affecting the outcome, patients were divided into those who survived and those who expired during the course of their illness. Data was analyzed using the SPSS version 12. The comparison of difference in means was calculated by student's t-test and the difference in proportions was compared by chi-square test of proportions. Results were expressed as mean and standard deviation. P-Value of <0.05 was taken as significant for all Statistical analysis.

Results

A total of 76 patients of FM were admitted during the two and half year's period from May 2003 to November 2005. Out of these, 36(47.36%) had jaundice on admission. One patient with hepatitis B infection was excluded. There were 29 (82.86%) males and 6(17.14%) females, aged between 14 and 70 years (Mean age 33.74±14.89 years).

Apart from fever and jaundice, which were present in all the patients, other signs and symptoms were related to individual complications. The important findings were, pallor 74.3%, impaired consciousness 62.9%, Hepatomegaly 77.14%, and Splenomegaly 54.29%. The other important associated manifestations were renal failure 62.9%, and cerebral malaria in 22.9%. Although impaired consciousness was present in 69.9%, only 22.9% patients fulfilled the WHO criteria for cerebral malaria. Most of the patients had at least one other manifestation of severe malaria other than jaundic.

Comparison of parameters between Group A and B are shown in Table 1 and 2.

Impaired consciousness, hepatomegaly and renal failure were most common and significantly associated with rising bilirubin. In Group- A only 27.23% patients had renal failure as compared to Group-B with high bilirubin where 77.27% patients developed renal failure. p= 0.001(Table1). The duration of illness ranged between 2 to14 days with a mean of 6.37±3.0 days.

Disease duration was positively correlated with rising bilirubin level. Group-B Patients with high bilirubin level had a mean duration of illness 8.05±2.77 days as compared to Group A, who had a bilirubin of between 3-10

Table 1: Comparison of clinical Parameters between the two groups.

Parameter No, (%)	Total no of Cases 35	Group-A Bilirubin 3-10 mg N=15 (42.86%)	Group-B Bilirubin >10 mg N=20 (57.14%)	P-value
Fever	35(100%)	15(44.12)	19(58.88)	0.394
Impaired consciousness	22(62.9%)	6(27.27)	16(72.73)	0.015
Anaemia	26(74.3%)	12(46.15)	14(53.85)	0.517
Oliguria or anuria	13(37.14%)	03(23.08)	10(76.92)	0.073
Hepatomegaly	27(77.14%)	9(33.33)	18(67.67)	0.037
Splenomegaly	19(54.29%)	11(57.89)	8(42.11)	0.052
Thrombocytopenia	28(80%)	11(39.29)	17(60.71)	0.408
Renal failure	22(62.9%)	05(27.23)	17(77.27)	0.001
Cerebral malaria	8(22.9%)	3(37.5)	05(62.5)	0.737
Disseminated Intravascular Coagulation	3(8.6%)	Nil	03(100)	0.124
Expired	14(34.3%)	03(21.43)	11(78.57)	0.037

mg / dl and had disease duration 4.13±1.50 days P= 0.001 (Table 2).

Serum transaminases, Prothrombin time (in seconds) and serum albumin were not significantly raised in comparison with rising serum bilirubin (Table 2).

Surprisingly in all patients serum ALT remained below 135 IU/L even when bilirubin was rising.

The mean value of serum ALT in patients with serum bilirubin 3-10mg/dl was 41±16 IU/L as compared to 53.46±31.24 IU/L in patients with serum bilirubin levels >10mg/dl (P=0.169). Eight patients (22.85%) had features of encephalopathy without focal neurological deficit, mimicking viral fulminant hepatic failure. The liver was palpable in all these patients and two of them had evidence of DIC. A high TLC count was noted in patients with high bilirubin. Significant correlation was found between rising bilirubin and parasite density P=0.01 (Table 2).

All patients received either Quinine or Artemether according to standard Protocol along with supportive therapy to deal with complications.

Of the total study patients, 14 (40%) succumbed to the disease while 21 (60%) had complete recovery. Comparison of parameters between the patients who survived and those who expired is shown in Table 3. Prolonged duration of illness was associated with high mortality.

In fatal group mean duration of illness was 7.99±3.15 days as compared to those who survived 5.57±2.64 days (P=0.025). Renal failure as evidenced by the derangement of renal function and showed significant correlation with mortality. Mean serum creatinine value in patients with adverse outcome was 8.64±4.39 mg/dl as compared to 4.18±3.18 mg/dl in those who survived (P=0.002). Deteriorating level of consciousness with low score on GCS, low platelet count, high serum bilirubin level on admission, deranged Prothrombin time, low serum albumin and high parasite count were associated

Table 2: Comparison of laboratory Parameters between the two groups.

Parameter	Group-A (N=15) Bilirubin 3-10 (mg/dl)	Group-B (N=20) Bilirubin>10 mg/dl)	P-value
Age.	29.47±11.02	36.95±16.79	0.144
Duration of illness (in days).	4.13±1.50	8.05±2.74	0.001
Temperature in F0	101.27±1.48	100.52±1.51	0.154
Serum total bilirubin (mg/dl)	4.79±1.35	20.67 ±7.37	0.001
Serum conjugated bilirubin(mg/dl)	2.91±1.60	16.53±6.85	0.001
Serum alanineaminotransferase (U/L)	41±16	53.46±31.24	0.169
Serum aspartate aminotransferase(U/L)	69.33±50.91	83.40±77.93	0.548
Alkaline phosphatase(U/L)	142.27±71.93	149.25±57.98	0.752
Serum total proteins(mg/dl)	6.46±0.59	6.39±0.56	0.702
Serum Albumin(mg/dl)	3.10±0.65	2.81±0.61	0.195
Prothrobin time in seconds	15.37±1.67	16.75±3.85	0.203
Haemoglobin(g/dl)	8.44±1.97	8.30±2.73	0.868
White blood cell count(×109/L)	6.4±3.09	10.27±4.11	0.004
Platelet count(×109/L)	81.27±82.64	62.45±41.17	0.384
Serum creatinine(mg/dl)	3.35±3.78	7.48±3.58	0.002
Blood urea (mg/dl)	127.50±102.89	277.75±104.74	0.001
Score on Glasgow Coma Scale	13.40±2.72	11.40±2.60	0.034
Parasite count in %	6.29±2.81	15.35±12.60	0.01

Table 3: Predictors of mortality in patients with jaundice due to falciparum malaria.

Parameter	Survived group (N=23) (65.71%)	Expired group (N=12)(34.29%)	P-value
Age.	32.87±14.48	35.42±16.14	0.63
Duration of illness (in days).	5.57±2.64	7.92±3.15	0.025
Temperature in F0	101.02±1.50	100.50±1.57	0.348
Serum total bilirubin (mg/dl)	11.23±8.26	18.90±10.87	0.026
Serum conjugated bilirubin(mg/dl)	8.68±7.76	14.54±9.15	0.055
Serum alanineaminotransferase (U/L)	42.04±18	59.75±35.49	0.057
Serum aspartate aminotransferase(U/L)	65.83±53.78	99.50±85.70	0.162
Alkaline phosphatase(U/L)	155.48±72.32	128.58±38.07	0.239
Serum total proteins(mg/dl)	6.56±0.54	6.56±0.54	0.044
Serum Albumin(mg/dl)	3.13±0.66	2.54±0.38	0.008
Prothrobin time in seconds	15.17±1.50	18.02±4.50	0.008
Haemoglobin(g/dl)	8.40±2.11	8.27±3.0	0.883
White blood cell count(×109/L)	7.82±4.04	10.13±4.08	0.119
Platelet count(×109/L)	87.91±69.52	37.16±21.25	0.020
Serum creatinine(mg/dl)	4.18±3.18	8.64±4.39	0.002
Blood urea (mg/dl)	181.28±111.53	274.83±137.35	0.037
Score on Glasgow Coma Scale	13.39±2.15	10.08±2.68	0.001
Parasite count in %	7.75±3.42	18.58±15.53	0.003

with adverse outcome, Table 3.

Discussion

Since times immemorial Falciparum Malaria continues to conjure up images of seriously ill patients presenting with Cerebral Malaria or Black Water Fever. Over the last two decades this face of malaria has changed radically with jaundice being the leading clinical presentation of complicated Falciparum Malaria. This fact needs to be propagated especially in those countries where other infectious illnesses leading to jaundice, such as viral hepatitis and fulminant hepatic failure (FHF) are also widely prevalent.

Due to the paucity of data on jaundice in severe Falciparium Malaria in adults, even in WHO guidelines, Jaundice is accorded only1+significance as a prognostic factor for severity of disease in adults, whereas circulatory collapse, pulmonary oedema and respiratory distress are assigned 3+significance.[3] Our study also clearly indicates that rising bilirubin is significantly related to mortality, even though the number of patients in this study is small (35 cases).

The incidence of jaundice in Falciparum Malaria is on the rise and has been reported to be between 2% to 57%.[9-11] In our study 47.36% patients had jaundice as a presenting symptom which is in accordance to the findings reported in other studies conducted in similar areas of malarial transmission. Physicians should be made aware of the more common emerging presentations of complicated Falciparum Malaria i.e. jaundice or acute renal failure in this study. As a matter of routine, jaundiced patients with altered consciousness and a short history are considered to have viral hepatitis rather than malarial hepatitis. This can be a fatal error in terms of prompt institution of appropriate therapy. Pakistan is an area of unstable endemicity for Falciparum Malaria. This results in a presentation which is complicated in children as well as in adults, particularly following the monsoon season of July and August.[12,13]

Over the years it was our impression that the depth of jaundice was directly proportional to the duration of fever prior to diagnosis of Faciparum Malaria and the institution of appropriate treatment. The time lag in presentation of patients with severe jaundice is almost double that of patients with relatively milder jaundice in this study. The delay in presentation was also significant when comparing patients who expired with those who survived. Presumably the longer duration of unbridled parasitaemia prior to diagnosis leads to higher parasite counts and profuse parasitization of all ages of erythrocytes. The sticky, knobbed parasitized red cells occlude micro-vasculature, leading to the more complicated forms of Falciparum Malaria, including severe jaundice. The increased depth of jaundice and high mortality linked with increased duration of illness in cases of falciparum malaria has been reported in the past studies.[2] In a case series of 212 hospitalized patients of falciparum malaria reported by Mozumdar et al[4] from Kolkata, the higher mortality of 75% was mostly in late presenters.

In our study majority (57.14%) of the cases had conjugated heperbilirubinaemia with milder elevation of liver enzyme (2-3 folds). In cases of severe falciparum malaria, conjugated hyperbilirubinaemai is a well known entity and serum ALT elevation is seen in few patients with levels more than 5 times normal being rarely

encountered.[14,15] Serum albumin level was also significantly lower in those patients who expired. This may reflect the acute phase reaction and may help in determining the prognosis on admission.

It is interesting to note that there was no significant difference in the mean haemoglobin level of the two groups of patients with mild and severe jaundice as well as between those who survived or succumbed. Despite the differences in parasite load baseline haemoglobin was also not statistically different between the two groups of patients with mild and severe disease. Hence the degree of haemolysis was not a significant factor in determining the severity of jaundice or indeed mortality. Intra-hepatic cholestasis or hepatic dysfunction/involement might therefore be a significant factor in patients with falciparum malaria and severe jaundice.[16]

There was a significant association of hepatomegaly and acute renal failure (ARF) with rising bilirubin levels. This elevation of bilirubin was typically an increase in conjugated bilirubin. The concomitant renal failure may contribute to the elevated conjugated hyperbilirubinemia by virtue of decreased excretion of conjugated bilirubin.[17] The co-existence of acute renal failure was highly significant in those with more severe jaundice and in all probability enhanced the likelihood of dying in this series of patients. An initial creatinine in excess of 8.6 mg/dl mg conferred a higher risk of mortality in this study. The strong association between renal failure and jaundice in falciparum malaria has been described previously in studies on falciparum malaria mainly from Asian countries.[6] Mortality has also been linked to acute renal failure.[6,18]

Although consciousness was impaired in almost 70% of cases in this study, only 23% had cerebral malaria as defined by WHO.[3] Furthermore the severity of bilirubin elevation was not significantly related to the occurrence of cerebral malaria, suggesting that different mechanisms are operative in the genesis of altered sensorium in these two types of patients, which could be a combination of hepatic dysfunction and renal impairment. Studies on patients with falciparum malaria with altered consciousness, have shown that the defined criteria could not be fulfilled for diagnosing cerebral malaria.[19] Nitya Nand et al also ascribed impaired consciousness in such patients to renal failure or electrolyte imbalance.[20]

The occurrence of thrombocytopenia in 80% of the patients of jaundice with Falciparum Malaria is an enigma and has been reported by many authors previously.[21] The presence of moderate thrombocytopenia in most cases of complicated Falciparum Malaria remains largely unexplained. The severity of thrombocytopenia was more significant in the fatal cases of our study. Hence initial platelet count could be a valuable prognostic indicator of the severity of illness at the time of presentation.[22] Even though the platelet count and prothrombin time were similar in the two groups of patients with moderate and severe jaundice; an analysis of fatalities showed a significant difference in parameters between those who died and those who recovered. This may also be partly explained by occurrence of DIC in those who expired.

No liver biopsies were done in this study as liver biopsies in all patients with suspected malarial hepatitis are not recommended except when the diagnosis cannot be resolved by other tests. However, histological changes in malarial hepatitis, pathognomonic and specific to this disease, can establish the diagnosis at any stage of the illness.[8,23]

Conclusion and Recommendations

The present study showed a high incidence of hepatic involvement, which indicates that falciparum malaria is one of the causes of severe jaundice in adult population in this part of the world. In patients presenting with fever and mainly conjugated hyperbilirubinaemia, there should be a high index of suspicion for falciparum malaria even in the face of negative blood films.

A combination of late presentation, altered sensorium, severe conjugated hyperbilirubinemia, prolonged prothrombin time, low albumin, elevated urea and creatinine and a low platelet count were significant predictors of adverse outcome in Falciparum Malaria.

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