Biochemical Findings in Severe Malaria: a Study on 100 Patients

*Hussain MF,[1] Ahmed MU,[2] Ahamad SU,[3] Faiz MA[4]

A prospective cross sectional study was conducted to find out the biochemical profiles in patients of severe malaria in Chittagong Medical College Hospital (CMCH). One hundred patients over 13 years of age irrespective of sex, race, religion and pregnancy were included purposively. Eighty patients (80%) were male. Male:female ratio was 4:1. The mean age (years) of the patients was 29.1± 11.4 and the range was 14 to 56years. Biochemical assessment was done by using i- STAT Ec8+ card (Abbott Limited, East WinsdorNJ, USA) and findings were hypoglycaemia (6%), hyponatraemia (25%), hypokalaemia (14%), hyperkalaemia (19%), Blood Urea Nitrogen (BUN)>60 mg/dl(34%), P^H <7.35(16%), HCO_3<15 mmol/L (27%), BE (base excess) >10 mmol/L (28%), anion gap>18 mmol/L (29%). 34% had acute renal failure (ARF), 28% had acidosis, and 24% had multiorgan dysfunction. Out of 100 cases with positive paracheck, 95 were smear positive and remaining 5 were negative. All the positive blood smear showed *Plasmodium falciparum* parasite.Out of hundred patient 69 patient (69%) recovered & 31patients(31%) had died. Two patients had recovered with complication (ataxia). Main causes of death were multi organ dysfunction, acute renal failure and acidosis. So, biochemical profiles could provide valuable clues for important pathophysiological process of severe malaria and may have significant clinical implication.

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Key words: Severe malaria, biochemical findings, multi organ dysfunction, acidosis.

Introduction

Malaria continues to be the world's most important protozoan - parasitic infection. Malaria occurs in 99 countries. An estimated 3.3 billion persons were at risk of malaria in 2010. Estimated malaria cases in 2010 were 216 million and reported deaths from malaria in 2010 were >3,00,0000. Approximately 86% of malaria deaths occurs in children under 5years of age and the majority of are in sub-Shaharan Africa. The estimated incidence of malaria decreased by 17% globally from 2000 to 2010 and the malaria mortality are decreased by 26% following increasing in prevention and treatment.[1]

Malaria is one of the major public health problems in Bangladesh. Out of 64 districts, 13 districts are in the high endemic areas of malaria transmissions. In these 13 endemic districts there are 70 endemic Upazillas (subdistrict level) covering 620 unions with

1. **Dr. Md. Farhad Hussain, Associate Professor, Department of Medicine, Cox's Bazar Medical College, Bangladesh. farhadsmc91@yahoo.com*
2. *Dr. Misbah U Ahmed, Assistant Professor, Department of Community Medicine, Cox's Bazar Medical College, Bangladesh*
3. *Dr. Shahab Uddin Ahamad Assistant Professor, Department of Pathology, Chittagong Medical College, Bangladesh*
4. *Professor M A Faiz, Dev Care Foundation, Bangladesh and Former Professor & Head of Medicine, Chittagong Medical College, Bangladesh*

**For correspondence*

the total population of 10.9 million. Over 98% of the total cases in the country are reported from these areas. In these 13 endemic districts total 48647 cases were reported in 2005 and total numbers of deaths were 501.[2] From July 2008 to May 2009 a total of 74,412 cases were diagnosed either by microscopy or RDT and treated according to National Malaria treatment protocol . Among them 62,347 cases were *P. falciparum* (84%), 11751 cases were *P. vivax* (16%) and 314 were mixed infection case. The interventions implemented so far have shown positive trends to decline death and increase the total number of cases. In July 2008 to May 2009 total cases are found 74412 and total deaths are 89, which are 6 times less death from 2005 and total cases are found almost 2 times more than 2005;[3] this is due to increase in case detection rate. A further decline in cases occurred with 29,518 cases in 2012 with 11 deaths.

Most of the patients of severe malaria have some biochemical abnormalities. So far we know, no such study on biochemical profile in case of severe malaria had been reported from Bangladesh. A small scale study in 60 patients was done in India. They used several clinical and biochemical parameter. Blood urea, serum creatinine, serum sodium, serum potassium, serum bilirubin, haematological profile was among the biochemical parameter.

We conducted a prospective cross sectional study of biochemical profile of severe malaria in Chittagong Medical College Hospital.

Methods

This study was carried out at the Chittagong Medical College Hospital (CMCH), Chittagong, Bangladesh during the period of June 2005 to June 2006. One hundred cases of clinically suspected severe malaria admitted to one of the medicine unit of CMCH were enrolled. The inclusion criteria were- 1) patient should have one or more clinical syndrome of severe malaria in patients over 13 years of age; irrespective of sex, religion and pregnancy & 2) positive Rapid dipstick (HPR-2) test for *Plasmodium falciparum* (parackeck).The patient who received quinine more than 40mg/kg before recording the information were excluded. After taking informed consent blood samples were collected and data were recorded. Biochemical investigation was done by using i – STAT Ec8+ card (Abbott Limited, East Windsor NJ, USA). Other investigations were done from available hospital facility and locally available private pathological laboratories. The patients were treated by parenteral quinine or artesunate. The data was analysed by computer based software program MS Excel and "Statistical Package for Social Sciences- SPSS 12."

Results

A total one hundred cases of clinically diagnosed and paracheck test positive severe malaria were studied during the study period. Total 321 paracheck test was done and 126 were positive. 26 positive cases were excluded due to different reason e.g. treatment with quinine more than 40 mg/kg before admission, did not give consent, technical error of the i-STAT tools etc.

Age range of enrolled patients was from 14 to 56 years. Mean (±SD) age of patients were 29.11 (±11.37) years (table I).

Table I: Age distribution of the patients (n = 100)

Age group (years)	Number	Range (Years)	Mean ± SD (years)
≤ 20	33	14 – 20	17.7 ± 1.7
21 – 30	29	21 – 30	25.7 ± 3.1
31 – 40	23	32 – 40	36.5 ± 2.6
41 – 50	11	45 – 50	47.5 ± 2.5
≥50	04	52 – 56	54.5 ± 1.7

This study included 80 male (80%) and 20 female (20%) patients. The male – female

ratio was 4:1. Out of 20 female patients, 4 were pregnant. One of them was primigravida and remaining three were multigravida. The primigravid patient had spontaneous abortion. All pregnant patients improved completely. Blood film for malarial parasite was positive in 95 out of 100 patients and all of which were *Plasmodium falciparum*.

Out of 100 cases 25 patients (25%) had hyponatraemia and two patients (2%) had hypernatremia. The mean (± SD) level of Na^+ on admission was 133.8 (±6.5) mmol/L, and range was 108 to 153 mmol/l. On admission 14 patients (14%) had hypokalaemia and 19 patients (19%) had hyperkalaemia. The mean (±SD) level of K^+ was 4.26(± 0.9) mmol/L and the range was 2.5 to 7.2 mmol/L (Table – II).

Table II: Biochemical findings of Na^+ & K^+ level

Findings	Number of the Patients	Percentage
Hyponatraemia	25	25
Hypernatraemia	02	02
Hypokalaemia	14	14
Hyperkalaemia	19	19

The mean (± SD) glucose level was 126.9 (± 51.7) mg/dl and range was 20-257 mg/dl. On admission six (6%) patients had hypoglycaemia. In this study, 33 patients (33%) had BUN above 60mg/dl and among them 5 patient had BUN >140mg/dl which indicate severe renal impairment. The mean (±SD) level of BUN on admission was 50.19 (±39.31) mg/dl and the range was 06 to > 140mg/dl. Mean level of serum creatinine was 2.88±1.11 mg/dl.In this study, P^H was done from venous blood sample. The mean P^H (±SD) was 7.38 (±0.10) and the range was 6.79 to 7.53. Sixteen patients had P^H < 7.35 and 20 patients had P^H >7.45.Out of 100 patients 27 patients (27%) had H CO_3 level less than 15mmol/l which indicate acidosis. Two patients had H CO_3 level more than 28mmol/l. The mean (±SD) HCO_3^- level was 18.9 (±5.4) mmol/l and the range was 02 to 29 mmol/l. BE>10mmol/l indicate acidosis. In this study mean BE was 7.27 ± 6.0mmol/l. 28 patients (28%) had BE>10 mmol/l (Table – III).

Table III: Biochemical findings of P^H, HCO_3^- & BE

Findings	Number of Patients	Percentage
P^H < 7.35	16	16
P^H > 7.45	20	20
H CO_3 < 15mmol/l	27	27
H CO_3 > 28mmol/l	02	02
BE > 10mmol/l	28	28

The mean (±SD) anion gap in this study was 17.4 (±4.9) mmol/L; and the range was 4.0 to 38.0 mmol/L. Out of 100 patients 29 patients (29%) was present with anion gap more than 18 mmol/L.

Table IV: Biochemical findings incase of severe malaria (n=100)

Findings	Number of the Patients	Percentage
Hyponatraemia	25	25
Hypernatraemia	02	02
Hypokalaemia	14	14
Hyperkalaemia	19	19
Hypoglycemia (Glu <45 mg/dl)	06	06
Renal impairment (BUN >60mg/dl)	33	33
P^H < 7.35	16	16
P^H > 7.45	20	20
H CO_3 < 15mmol/l	27	27
H CO_3 > 28mmol/l	02	02
Anion gap >18mmol/l	29	29
BE >10 mmol/l	28	28

Outcome

Out of 100 patients sixty nine (69%) patients recovered and thirty one (31%) patients died.

Most of death were due to multiorgan dysfunction, renal failure and acidosis (Table V).

Table V: Outcome of severe malaria patients (n= 100)

Outcome of patients	Number of patients	Percentage
Recovered without complications	67	67
Recovered with complications	02	02
Death	31	31
Total	100	100

Discussion

One hundred cases of severe malaria were investigated during the study period. Among them 80 were male and male female ratio was 4:1. Male may acquire more infection because of their outdoor life. Mean age of the cases were 29.1 ± 11.4 years and the range were 14 to 56 years. Out of 20 female patients, 4 were pregnant. One of them was primigravida and was in first trimester. The primigravida patient had spontaneous abortion. All the pregnant patient had improved completely. The mortality in pregnancy due to malaria was found high in different studies in Bangladesh and abroad. In one study in the same hospital by Rahman et al,[4] the case fatality rate of malaria in pregnancy was 40%. But it is not consistent with the present study, may be because of small size of pregnant patient studied. Falciparum malaria in pregnancy carries increase risk to mother and foetus[5].

The mean duration of present illness before hospitalization was 7.5 ± 5.3 days and the range were 2 to 30 days. The mean duration of severe illness before hospitalization was 2.46 ± 1.8 days and the range were 0.5 to 8.0 days. Duration of severe illness were longer before hospitalization in deaths than in survivors.

Out of 100 paracheck positive severe malaria patient 95 patient showed malaria parasite in blood smear. All were P.falciparum. Parasite count ranges from 5,600 to 460,000/cumm. High parasite count was associated with poor outcome. Negative blood smear may be due to prior anti-malarial treatment or due to parasite sequestration in the microvasculature. But falciparum malarial antigen HRP-2 may present in blood for few weeks of malarial attack and can be detected by paracheck test. Almost all of the biochemical findings were detected by i-STAT Ec8+card within 2 minutes. These were detected at the time of presentation during hospitalization.

25 patients had hyponatramia and 2 patients had hypernatraemia. Mean level of Na was 133.8 ± 6.5 mmol/L. Hyponatremia is a common findings in severe malaria and relates to dehydration[6]. Some studies claim a role for inappropriate ADH secretion in severe malaria, but this is controversial.[7] In malaria there is mild increase in systemic capillary permeability, which may contribute to hyponateraemia by lowering plasma albumin levels.[8] Mean level of potassium was 4.26± 0.9 mmol/L and the range was 2.5 to 7.2mmol/L. 14 patient had hypokalaemia and 19 had hyperkalaemia. Blood urea nitrogen (BUN) is one of the indicator of renal insufficiency. It's value above 60mg/dl indicate renal insufficiency. Deranged renal functions like rise in blood urea and creatinine in malaria have been attributed to various factors like dehydration, catabolism and impaired renal function[9]. In this study 34 patient (34%) had BUN>60mg/dl on admission. The mean value was 50.2± 39.3mg/dl. (S. Creatinine was 2.9 ± 1.1mg./dl). 19 out of 31 deaths (61%) had acute renal failure (ARF). Among the 19 deaths 15 had multi-organ dysfunction. A study by Dey et al[10] on 346 adults with severe malaria, 27% cases had acute renal failure. Present study is almost consistent with that

study. Acute renal failure is a major cause of death in adult patients with severe falciparum malaria.[11] Acute renal failure results from acute tubular necrosis.[12] Acute tubular necrosis presumably results from renal microvascular obstruction and cellular injury consequent upon sequestration in the kidney and the filtration of free hemoglobin, myoglobin and other celluler material. Significant glomerulonephritis is very rare.[13] Many patients are dehydrated when first admitted to the hospital and in some of them the renal function is restored to normal by simple rehydration.

Acidosis is an important cause of death in severe falciparum malaria. According to the WHO's 1990 definition – acidaemiae defined as arterial or capillary P^H <7.35 or acidosis defined as a plasma bicarborate concentration <15mmol/l or a base excess >10mmol/l. In this study, 16 patients had P^H <7.35, 27 patient (27%) presented with HCO_3<15mmol/l and 28 patient (28%) with BE (Base excess)>10mmol/l. So, 28% patients were suffering from acidosis. Out of 31 deaths,19 patients were acidotic and mortality rate was 61%. Most of the acidotic patient had other organ involvement. Acidosis also associated with high anion gap. In this study 29 patient were presented with wide anion gap (anion gap >18 mmol/L) Several factors contribute to acidosis in severe malaria. It is associated with hyperlactatemia, originating mainly from anaerobic glycolysis. This is thought to result from local tissue hypoxia caused by obstruction of the micro-circulation associated with parasitized erythrocyte sequestration and increased rigidity of circulating erythrocytes.[14-16] Decreased hepatic clearance of lactate and to a much smaller extent parasite production of lactate also contribute.[14,17,18] An important contributor to acidosis in malaria is acute renal failure, particularly in adult patients.[14]

In this study out of 100 patients 69 recovered and 31 patients had died. So case fatality rate 31%. Most of the death occurred due to multi-organ dysfunction, acidosis and renal impairment. Severe malaria carries a treated mortality of approximately 20%.[19,20] In our study, it is around 30% which is consistent with present study. The high rate of mortality may be due to lack of ICU facility. If biochemical abnormalities in a severe malaria patient detected earlier prompt correction can be done which can save many life.

Conclusion

Malaria is one of the most common parasitic disease causing morbidity and mortality in the tropics. The possible pathogenic mechanism are hyperparasitaemia with sequestration in the internal organs, intravascular haemolysis and immune mediated; role of cytokines mediated for injury has also been documented.

In this study, significant number of patient had electrolyte disturbances which were not too much severe. Hyponatremia was a common findings in severe malaria. This study confirms the importance of acidosis in the pathophysiology and outcome of severe adult malaria and suggest a multi-factorial origin. Involving tissue hypoxia resulting from parasite sequestration, liver dysfunction and renal impairment, here the indicator were p^H, Serum bicarbonate, Base Excess, and anion gap. Lactic acid may be the main acid responsible for acidosis. But other unidentified anion may also be responsible.So biochemical profiles could provide valuable clues to important pathophysiological process of severe malaria and may have significant therapeutic implications.

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