PROFILE OF SEVERE FALCIPARUM MALARIA IN DIABETICS

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ABSTRACT

Clinical profile of severe falciparum malaria in diabetics was compared with non-diabeties. 76 patients of severe falciparum malaria with diabeties and 72 non diabetics were enrolled in this study. The diagnosis of severe falciparum malaria and diabetes mellitus was made in accordance with WHO guidelines. The detailed clinical work up was done in all cases. Blood was collected for hematological and biochemical investigations. The results showed that 17.4% patients of malaria had diabetes mellitus. Absence of fever at the time of admission was found in 21% diabetic patients with malaria. Multi-organ involvement was more common (15.1%) in diabetics. Relative bradycardia, hypoglycemia at the time of admission and diabetic ketoacidosis was present in 26.3%, 8.3% and 2.6% cases respectively. The coma-onset time was shorter and duration of coma was longer in diabetics. The mortality was higher (34.2%) in diabetics. After administration of quinine, side effects like hypoglycemia and cardiac arrhythmia were present in 7.8% and 5.2% cases respectively. This study showed that multi organ dysfunction was present in 15.4% cases. It also showed that atypical presentations like absence of fever, presence of hypoglycemia and keto acidosis could delay the diagnosis and treatment, which may cause higher mortality. In view of the quinine-induced toxicity, its should be used with caution in diabetics. The dose of insulin should be reduced while treating such patients with quinine.

KEY WORDS : Falciparum malaria: Diabetes mellitus: Complications; Treatment.

INTRODUCTION

Diabetes mellitus is one of the most common non communicable diseases and malaria is the commonest vector borne parasitic disease of the globe (1,2). There is also evidence that diabetes mellitus is going to be an epidemic in many developing and newly industrialized nations (1), whereas malaria is already an epidemic in 103 countries around the globe, with more than 2.5 billion people at risk and causes 1 to 3 million deaths anually (3). In spite of phenomenal progress in medical science, both continue to be the major killers (4). As both the diseases are common in developing countries, including India, it is not unlikely to come across diabetic patients with malaria. While treating patients of severe falciparum malaria with diabetes mellitus we observed uncommon presentations, unpredictable outcome and difficulties during treatment. Therefore, this prospective observational study was designed to study the profile of severe falciparum malaria in diabetics.

MATERIAL AND METHODS

The study was carried out at M.K.C.G. Medical College and Hospital, Ganjam, Orissa. It serves both as a hospital for local people and a referral hospital for adjacent eight districts. The study area is characterised by endemic and seasonal malaria.

This is a prospective, observational study on severe falciparum malaria. A pilot study was performed from January 1995 to December 1995 to gather preliminary information to develop a plan for the study. From January 1996, consecutive patients of smear positive, complicated falciparum malaria were enrolled in the study. Patients of complicated falciparum malaria with diabetes mellitus (DM) enrolled between January 1996 to December 1999 constituted the material for the present study.

The diagnosis of severe falciparum malaria was made in accordance with the WHO malaria action programme (5). The diagnosis of diabetes mellitus was made by following the1985 WHO criteria e.g. fasting glucose concentration $\geq$7.8mmol/l, a 2 hour glucose concentration of $\geq$11.1mmol/l, or the use of glucose lowering medication (oral agents or insulin)(6).

Giemsa stained, peripheral blood smear was used for detection and diagnosis of falciparum malaria.

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After hospitalisation, detailed clinical work up was done. The level of consciousness was assessed by Glasgow coma scale. The coma onset time (COT) and duration of coma (DOC) was determined in all cases. The COT was defined as the time interval from onset of fever to onset of coma and DOC as the time interval from initiation of coma to regaining of consciousness. Blood was collected for complete blood count and biochemical investigations like blood glucose, urea, creatinine, bilirubin, AST, ALT. Urine analysis along with tests for ketone bodies was done at the time of admission. CSF analysis was made to exclude meningitis in the patients with cerebral malaria. ECG, X-ray chest, abdominal ultrasonography, serum electrolytes and blood gas analysis was done when necessary. Depending on the clinical requirements, the investigations were repeated. Parasitic count was done by the formula (number of parasites per 200 WBC X total leukocyte count)/200. It was repeated 12 hourly to determine parasitic clearance.

Patients with previous record of renal failure, hepatic involvement, with evidence of infections like pneumonia and urinary tract infection, were excluded from the study. The patients were treated with parenteral quinine dihydrochloride with a loading dose of 20 mg/kg. body weight, followed by 10 mg/kg. at 8 hour intervals. Oral quinine was administered when they became fit to take it orally. 72 age and sex matched patients of severe falciparum malaria without diabetes mellitus were taken as controls.

Statistics

SPSS statistical software for Windows (Version 6, Chicago) was used for analysis (7). Difference between malaria with and without diabetes were tested by t test. The non-parametric values were analysed with one-way ANOVA. The survival analysis was made by Kaplan Meier survival analysis. P value of < 0.05 was considered to be statistically significant.

RESULTS

During the study period, 624 patients of complicated falciparum malaria were admitted, of which 92 patients (17.4%) had diabetes mellitus. The patients who did not meet the inclusion criteria and had missing data, were excluded from the analysis. Hence only 76 patients of malaria with diatetes were included (Group A). 72 patients of malaria without diabetes (Group B) were selected for comparison.

There were 8 patients (10.4%) in whom diabetes was detected for the first time wih an attack of severe malaria, whereas the rest 68 (89.1%) patients had the disease for a duration of 1 to 8 years. Type 1, type 2, and malnutrition related diabetes mellitus (MRDM) constituted 2 (2.6%), 62 (81.5%), and 4 (5.2%) patients respectively. As majority of patients of DM were in the age group of 41 to 50 years and majority of adult patients of malaria were found in 21 to 30 years, accordingly 72 patients of Group B were selected for comparison by the SPSS statistical software (Table-1).

Table 1: Age and Sex Distribution of Severe Falciparum Malaria

Age in	Diabetics			Non-Diabetics			Significance
Years	Male	Female	Total	Male	Female	Total	
15-20	3	2	5	3	1	4	NS
21-30	6	3	9	6	2	8	NS
31-40	5	2	7	6	3	9	NS
41-50	20	12	32	18	10	28	NS
51-60	10	8	18	12	8	20	NS
>60	4	1	5	2	1	3	NS
TOTAL	48	28	76	47	25	72	

The clinical features of patients of diabetes with malaria are presented in Table 2. History of fever was absent in 21% of patients of Group A compared to 2.7% of Group B ($p<0.001$). Relative bradycardia was found in 26.3% cases in Group A compared to 11.1% cases of Group B ($p<0.001$). Two patients (2.6%) of Group A presented with ketosis in the absence of any other infection. Multiorgan involvement was present in 12 (15.7%) cases ($p<0.05$). Hypoglycemia was detected in 6 (8.3%) cases of Group B whereas 2 (2.6%) cases of Group A presented with hypoglycemia in spite of a record of hyperglycemia and omission of oral hypoglycemic agents on the same day, before hospitalisation. The coma onset time (COT) was significantly shorter in the patients of Group A (33.7 ± 20.1 hours) compared to Group B (57.3 ± 33.3 hours). The mean duration of coma (DOC) was 90.0 ± 28.4 hours in Group A compared to 38.4 ± 22.3 hours in Group B. The haematological and biochemical parameters were shown in Table 3. Blood glucose, urea, serum creatinine, serum bilirubin values were more and serum albumin was significantly less in Group A patients.

Table 2: Clinical Presentation

	Diabetics (n=76)		Non-Diabetics (n=72)		Significance
	No.	%	No.	%	
Absence of Fever	16	21.1	2	2.7	p<0.001
Convulsion	4	5.2	3	4.1	NS
Unconsciousness GCS<5*	50	65.7	45	62.5	NS
Disorientation	10	13.1	8	11.1	NS
Oliguria	6	7.8	2	2.7	NS
Jaundice	10	13.1	8	11.1	NS
Black Water Fever	1	1.3	4	5.5	<0.05
Diarrhoea	4	5.2	2	2.7	NS
Vomiting	25	32.8	10	13.8	<0.05
Relative Bradycardia	20	26.3	8	11.1	<0.001
Hypoglycemia	2	2.6	6	8.3	<0.05
Multiorgan Involvement	12	15.7	8	11.1	<0.05
Ketoacidosis	2	2.6	0	0	<0.001

** GCS- Glasgow coma scale <5*

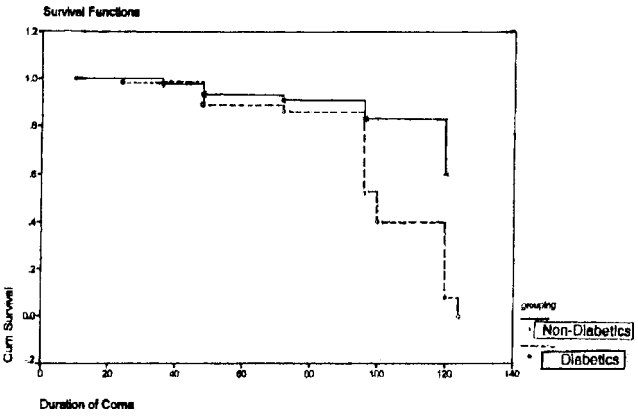
Table 3: Biochemical Parameters

Profile	Diabetics	Non-Diabetics	Significance
B. Glucose (mg/dL)	110.4±21.2	76.2±16.1	<0.001
B. Urea (mg/dL)	40.4±27.5	21.2±6.4	<0.05
S. Creatnine (mg/dL)	1.8±1.5	0.46±0.25	<0.05
Biluribin (mg/dL)	2.5±3.2	0.46±0.18	<0.05
Albumin (gm/dL)	2.5±3.2	0.46±0.18	<0.05
Haematocrit (%)	33.0±7.1	30.5±5.3	<0.05
Parasite count/mL	2058.2±212.2	4560±1195	<0.05
Platelet count (Lakh/mL)	1.4±0.05	1.6±0.56	NS

All patients were treated with quinine dihydrochloride. After quinine administration 6(7.8%) patients of Group A developed hypoglycemia compared to 3(4.1%) patients of Group B (p<0.05). Four patients (5.2%) of the former group showed ECG abnormality in the form of ventricular ectopics (n=2) and prolonged QT interval (n=2), whereas no abnormality was detected in the latter. Those patients with ECG abnormalities were treated with parenteral artesunate. For the control of hyperglycemia, soluble insulin was administered six hourly with estimation of blood/plasma glucose before each dose of insulin. The dose of insulin was modified depending on the glucose level.

The parasitic count was 2058.65+212.2/γ L in Group A compared to 4560.75 ±119.5/γ L (p<0.001). The Kaplan-Meier survival curve was constructed for comparison of Group A and B using time to death as the primary outcome. It showed that the mean ± SE of survival time was less in Group A (127.5 ± 7 Hr.) compared to Group B (143 ± 6 Hr.) (Log rank 4.35, df-1, p=0.0369), Fig-1.

Fig. 1 : Kaplan Meier Survival Curve in Group A and Group B.



DISCUSSION :

As seen in clinical practice, DM is frequently associated with infections. Of them bacterial, viral and fungal infections are common (8). Since little information is available on profile of falciparum malaria infection in diabetics, the present hospital based study is of interest.

The study showed that out of all cases of severe falciparum malaria, 14.7% were diabetics. In eight patients (10.4%) of severe malaria, DM was detected for the first time. Absence of history of fever was found is 21.1% cases. These patients presented with some abnormal finding (as explained by the attendants) and sudden loss of consciousness. Absence of fever may be due to depressed immunity in DM (8). Clinical suspicion of cerebral malaria in diabetics becomes difficult in the absence of history of fever. Hence, routine peripheral blood smear examination should be done in patients of DM with loss of consciousness especially in endemic areas of malaria.

The mean parasitic count in diabetics was less than in nondiabetic malaria patients. In experimental malaria (in mice), slow parasitic multiplication has

been observed (9). This may be the explanation of the low count. However, there was no difference in parasitic clearance time. Relative bradycardia was another clinical finding found commonly in diabetics. It has been observed in malaria with or without cardiac involvement (10,11). In diabetics, cardiovascular involvement does occur as a vascular complication (12). Probably this may be the cause of increased incidence of relative bradycardia in diabetics with malaria.

Diabetic ketoacidosis (DKA) was found in 2 patients of type 2 DM with falciparum malaria without any bacterial infection in this study. Ketosis, precipitated by falciparum malaria has already been reported (13). Though bacterial infection remains the most common precipitating factor of DKA world wide, malaria has been emphasized as a precipitant in developing countries (14). Therefore, in tropical countries, malaria should be looked for in patients with DKA.

Hypoglycemia was another complication found in 2(2.6%) patients of DM with malaria, before quinine administration in this series. Unexplained hypoglycemia caused by falciparum malaria in patients of DM before initiation of quinine therapy had been reported (15,16). In diabetic animal models, malaria infection dramatically lowers the blood glucose (9). Hence, associated malaria infection may be considered in a patient of DM with hypoglycemia.

Of the severe manifestations, cerebral malaria is the commonest form encountered in diabetics followed by multiorgan dysfunction. One of the pathogenic mechanisms of severe falciparum malaria is the interference in microcirculation by the aggregated and sequestered red blood cells (17). In a metabolic disease like DM, functional impairment of organs like kidney and heart are frequently found due to vascular involvement (11). In such a clinical condition, P. falciparum infection aggravates the organ dysfunction by interfering with the microcirculation. Probably this may be the explanation for the higher incidence of cerebral and multiple organ involvement in DM with malaria.

The treatment of DM with falciparum malaria is a challenge, because such cases will require insulin for control of hyperglycemia and quinine for treatment of malaria. Hypoglycemia and cardiac arrhythmias are commonly encountered side effects of quinine therapy in diabetics, compared to nondiabetics ($p<0.05$). Hypoglycemia is a major complication of falciparum malaria, and is associated with inceased mortality in patients with cerebral malaria (18). Hypoglycemia is caused by stimulation of insulin release by quinine (18). The additive effect of exogenous insulin administered for control of hyperglycemia may be the cause of higher incidence of hypoglycemia. Hence, blood glucose should be estimated before each dose of insulin and during quinine infusion. Therefore, in DM with falciparum malaria, insulin dose may be reduced or even omitted during quinine therapy, due to the potential threat of hypoglycemia. This is contrary to other associated bacterial infections in DM where the requirement of insulin is more than the previous dose. Apart from hypoglycemia, ECG abnormalities were detected in 4(5.2%) patients with quinine therapy. In view of these complications, one should be careful while treating such cases.

The mortality of severe malaria with DM was 34.2% which was more than nondiabetics (22.2%). The higher mortality may be due to short COT, prolonged DOC, multiorgan dysfunction, underlying organ dysfunction and autonomic neuropathy due to DM. The later may be the cause for sudden death found in 8 (30.6%) patients of malaria with diabeties.

The current study, the largest reported series on falciparum malaria with DM, showed that the profile of malaria is different from malaria without DM. It showed that absence of fever, presence of hypoglycemia and ketoacidosis, could delay the diagnosis of malaria and its treatment. This may be the cause of higher mortality. The treatment of such cases is also a challenge for the treating physician because of the effect of the parasites and antimalarials particularly quinine on glucose homeostasis.

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