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Prognostic value of blood glucose levels at the time of admission in complicated malaria

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Abstract
Occasionally malaria present with unusual symptoms and signs. Malaria is still the commonest cause of fevers requiring hospitalization in tropical area. A series of 1189 cases of fever with chills and rigors was studied, but only 80 cases have been included in this study for various reasons. The overall incidence of hypoglycemia in patients with severe falciparum malaria is likely to be high. But the diagnosis in such patients poses obvious difficulties. Changes in level of consciousness or depending coma, are usually attributed to cerebral malaria, and other signs such as sweating and tachycardia are common similar to hypoglycemia. There were three deaths (37.5% mortality) in cerebral malaria with hypoglycemia group. The three deaths are because of old age with ARDS, Acute renal failure and severe hepatic involvement respectively. As hypoglycemia is associated with severe malaria and high mortality our aim is to catch the attention of physicians on this entity.

Keywords: plasmodium falciparum, cerebral malaria, hypoglycemia

1. Introduction

William Osler

The word 'malaria' comes from Italian, and means literally 'bad air'. In 1894, Manson hypothesized that mosquitoes transmit malaria [1].

Following this hypothesis, in 1897, a young Scottish Physician in the Indian Medical Service, SIR RONALD ROSS Identified the dapple winged anopheles mosquito as the vector of human malaria. After a significant decline in the 60's, Malaria reemerged once again as a major health problem of India in the late 80's and presently it poses a major challenge with 20 to 25 lakhs cases annually. P. vivax is still the commonest (60-70%) followed by P. falciparam (30-45%) [2].

Mechanism of hypoglycemia

1. Glucose consumption may be increased in patients with malaria as a result of fever, infection and anaerobic glycolysis. In the host tissues malarial parasites also needs glucose for its survival. Parasites index increases glucose needs also increases.
2. The cinchona alkaloids quinine and quinidine release insulin from the pancreatic islet cells and this reduces hepatic gluconeogenesis and increases peripheral glucose uptake by tissues resulting in hypoglycemia.
3. Impaired hepatic function, due to malarial hepatitis, may reduce gluconeogenesis[3]
4. Glycogen reserves may be depleted especially in children and pregnant woman as a result of fasting and 'accelerated starvation' inhibition of gluconeogenesis by TNF and other cytokines could be the cause of a common hypoglycemia syndrome in children with severe malaria.

It occurs, commonly in the following three situations

1. Severe falciparum infection, especially in young children [4, 5, 6, 7].
2. Pregnancy with falciparum malaria, adult patients with severe disease [8].
3. Treatment with quinine (or quinidine) as a result of drug induced hyper Insulinemia [9, 10, 11, 12].
4. Prolonged depletion of food during high fevers.

In pregnancy, hypoglycemia may develop even without severe falciparum infection or treatment with quinine. Patients may have sweating, anxious, feeling of coldness, breathlessness, confusion, dilatation of pupils, labored and noisy breathing, tachycardia, convulsions and if protracted, coma. It may be easily confused with cerebral malaria. Hypoglycemia can cause fetal bradycardia and fetal distress. Treatment with 25-50% dextrose injection results in a dramatic recovery and prognosis in these patients is generally good.

2. Aims of the study

The present study was undertaken with an aim:

- To study the incidence of hypoglycemia in acute severe falciparum malaria and vivax
- Malaria.
- To assess the prognosis of acute severe malaria in relation to the hypoglycemia.
- To know the importance of blood glucose levels on and after admission of patients with acute severe malaria and its effect on proper treatment of hypoglycemia.
- To determine whether hypoglycemia was associated with other complications which may cause morbidity and mortality?

3. Materials and methods

All cases of malaria, diagnosed by peripheral smear examination, were prospectively studied at Osmania Hospital, Hyderabad, Department of Medicine. 1851 patients complaining of fever with chills and rigors were admitted and examined for evidence of malaria. Patients having evidence of all types of malaria were included in the study. After thorough clinical and biochemical examination the patients are categorized as 1. Malaria. 2. Simple falciparum malaria, 3. Complicated malaria. Bleeding time, clotting time, prothrombin time and platelet count were done in patients

showing evidence of bleeding tendency. Upper Gl endoscopy was done in all patients having hematemesis.
Special attention was given for blood glucose examination in all patients before starting I.V. therapy, as and when required. Blood glucose measurement was done by GOD/POD glucostix method. Blood glucose levels below 70mg% were considered as hypoglycemia as per American Diabetes Association guidelines.
Patents with prior history of Intravenous glucose administration were excluded.
All patients having Jaundice were tested for Australia antigen (HBsAg) and only HbsAg negative patients were included.
Hematological and biochemical parameters were obtained at diagnosis and at the remission of symptoms or disappearance of parasitemia.

Lab data

- Haemogram
- Peripheral blood smear for malarial parasite
- Urine Examination-
- Albumin, Microscopy - Red cells, Haemosiderinuria, Myoglobinurea.
- Biochemical parameters: Blood sugar, renal parameters, Serum Electrolytes, DIC Profile

Liver function tests
Other relevant parameters

- Arterial Blood gas analysis (ABG)
- X-ray chest PA View
- CSF analysis
- CT scan Brain
- Blood and urine cultures

4. Results

A total of 189 patients were admitted with fever with chills and rigors in various medical wards of Osmania Hospital, Hyderabad. Eighty patients were found to have malaria rest of the patients had various diseases.
Out of 80 patients of malaria 52 had plasmodium vivax trophozoites. 3 patients of this group had hypoglycemia. They have responded well with I.V. dextrose and antimalarial treatment. There is no mortality in this group of patients
Out of Eighty patients 28 had P. falciparum malaria in this 18 were males and 10 were females. One female was pregnant and another was in postpartum period. Both had pretreatment hypoglycemia. Fifteen cases were presented as acute severe falciparum malaria with coma. Rest of the patients had different complications such as hepatic involvement, severe anemia, algid malaria, ARDS and renal failure.
Out of Fifteen patients who were comatose, 8 patients had blood glucose level less than 70mg% at the time of admission. Out of 8 patients 3 had hypoglycemia as a cause of unconsciousness and they became fully conscious after infusion of 25% dextrose. Further line of management in these patients was oral or injection chloroquine/quinine/artesunate and symptomatic treatment was given and they completely recovered. The other 5 patients remained unconscious even after correction of hypoglycemia. These were the patients of cerebral malaria and were treated accordingly. Out of these 5 patients 3 expired, due to one from old age with ARDS another from renal failure and another patient from hepatic involvement 2 patients recovered completely.

Table 1: Sample composition (falciparum malaria)

Total Number of patients	28
Age Group	14-65
Male: Female	18:10
Mixed Infection	4
Pregnant females	1
Postpartum females	1

Table 2: Total Patients with malaria 80

		No. of patients	Euglycemia (%)	Hypoglycemia (%)
1.	Vivax Malaria	52	49 (94.24%)	3 (5.76%)
2.	Falciparum Malaria	28	20 (71.43%)	8 (28.57%)

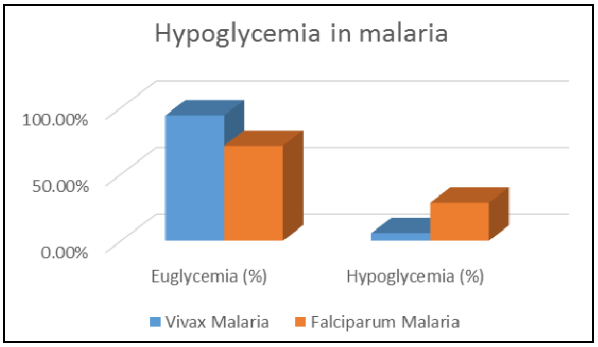

Fig 1: Hypoglycemia in malaria

Table 3: Survival rate in Falciparum malaria with Hypoglycemia

Total patients with hypoglycemia	8	
Recovered	5	(62.5%)
Death	3	(37.5%)

All patients (Twenty patients) with Euglycemia were recovered with antimalarial treatment, there is no mortality noted.

Table 4: Falciparum Malaria, blood glucose levels Outcome

Blood sugar level	No. of patients	Survived	(%)	Died	(%)
<70	8	5	(62.5%)	3	(37.5%)
>70	20	20	(100%)	0	(00.00%)

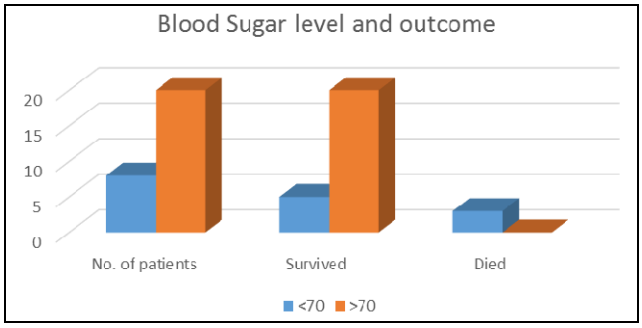

Fig 2: Blood Sugar level and outcome

Table 5: Various presentation of plasmodium falciparum

Presentation	No. of cases	Percentage
Fever + chills & regors	28	100
Coma	15	53.57
Sezures	5	20
Jaundice	18	64.4
Oliguria	14	50
Abdominal pain	8	28.5
Vomiting	1	3.5
Dyspnoea	1	3.5
Myalgias	1	3.5

Table 6: Complications associated with falciparum malaria

Complications	No. of cases	Percentage
Cerebral Malaria	12	42.85
Hypoglycemia	8	28.6
Anemia	23	82
Acute renal failure	16	57
ARDS	2	7
Thrombocytopenia	1	3.5
Hepatic Involvement	15	53.57

Table 7: Sr. Creatinine: Falciparum Malaria

S. creatinine	No. of patients	Percentage
< 1.5mg/d	11	39.28
1.5-3	4	14.28
3-6	7	25.00
6-10	4	14.28
> 10	2	7.00

Table 8: Serum Bilirubin in Falciparum Malaria

S. Bilirubin (mg/dl)	No. of patients	Percentage
0.5-3	7	25.00
3-5	6	14.2
5-10	10	35.71
Greater than 10	5	17.8

Table 9: ALT in Falciparum Malaria

ALT	No. of patients	Percentage
35-100	7	25
100 -350	20	71.42
>350	1	3.5

Table 10: AST in Falciparum Malaria

AST	No. of patients	Percentage
35-100	8	28.6
100 - 350	20	71.42

Table 11: Prothrombin time in Falciparum Malaria

P.T	No. of patients	Percentage
Normal	21	75%
Increased	7	25%

Table 12: CSF glucose in Falciparum Malaria

CSF glucose	No. of patients	Percentage
<40	8	28.57
40-70	20	71.42
Greater than 70	0	00.00

5. Discussion

Hypoglycemia is an important accompaniment of severe falciparum malaria and has a great influence on ultimate outcome of cerebral malaria. Timely recognition and proper correction may save the life of a person who is in deep coma due to hypoglycemia only, as P. Falciparum malaria with hypoglycemia and cerebral malaria are sometimes indistinguishable clinically at the time of admission [13]. Simple correction of hypoglycemia by 25% dextrose may bring the patient from unarousable coma to a fully conscious level [14].

The various possible mechanism of hypoglycemia in malaria are: Increased glucose consumption by malaria parasite and glycogen depletion / impaired glucogenesis, pregnancy and childhood due to prolonged fasting during high fevers, quinine induced hyperinsulinemia leading to hypoglycemia.

Three out of 8 patients with blood glucose level less than 70mg% presented in deep coma and were saved by proper recognition and early management of hypoglycemia.

K ocher DK, Kumawat BL [14] raised a vital question that definition of cerebral malaria should also include “exclusion of hypoglycemic encephalopathy" at the end of definition given by WHO and Warrel and Cowarkers [15]. Also they have stressed the need of blood glucose examination in all the patients at the time of admission. This may also prove beneficial to separate the comatose patients in two different categories i.e. cerebral malaria v/s P. falciparum malaria with hypoglycemia, which is very difficult to decide clinically. Its importance is further emphasized because the treatment priorities of both the conditions are different. Administration of IV quinine in the patients of later group may further increase the severity of hypoglycemia and facilitates the adverse outcome.

The overall incidence of hypoglycemia in patients with severe falciparum malaria is likely to be high. But the diagnosis in such patients poses obvious difficulties. Changes in level of consciousness or deepening coma, are usually attributed to cerebral malaria, and other signs such as sweating and tachycardia are common.

In a study of adult patients from Thailand, 8% of patients with severe malaria were hypoglycemic. This was a problem particularly in pregnant woman, 50% of whom were hypoglycemic [18].

Hypoglycemia is even more common in African children, occurring in 32% and 23% of cases of cerebral malaria reported in the Gambia [20] and Malawi [16] respectively.

Kocher *et al* [19] have reported that 11 out of a total of 532 cases of severe and complicated malaria had hypoglycemia (blood glucose less than 70mg/dl). Thus 2.06% of their cases had hypoglycemia.

In our study 8 patients out of 28 patients of acute severe falciparum malaria had hypoglycemia. Thus 28.5% of our cases had hypoglycemia coinciding with the results of Gambian and Malawian studies [20].

Brewster DR. *et al* [17] shown that the hypoglycemia is an important prognostic factor, in their study, there was greater than 40% mortality in cerebral malaria with hypoglycemia when compared with around 7% in cerebral malaria without hypoglycemia.

In our study also there is 37.5% mortality in cerebral malaria with hypoglycemia. This was because of cerebral malaria associated with other complications like ARF, hepatic

involvement and elderly age, in cerebral malaria without hypoglycemia there is no deaths.

Although the correction of hypoglycemia in cerebral malaria rarely leads to an immediate improvement in the level of consciousness, it requires immediate correction as soon as it is detected as other therapeutic maneuvers introduced will not be able to show their true effect in patients who are allowed to remain hypoglycemic.

The most important clinical variables at admission that predicted development of hypoglycaemia after admission were hypoglycaemia, severe anaemia and temperature gradient (a marker of impaired perfusion or circulatory failure).

6. Summary & Conclusion

A series of 189 cases of fever with chills and rigors was studied, but only 80 cases have been included in this study for various reasons.

At attempt has been made to evaluate blood sugar levels at the time of admission and its possible prognostic value of hypoglycemia in acute severe malaria which is an increasingly a common disease and diagnostic problem in cerebral malaria.

This may also prove beneficial to separate the comatose patients in two different categories i.e. cerebral malaria v/s P.falciparum malaria with hypoglycemia, which is very difficult to decide clinically. Its importance further emphasized because the treatment priorities of both the conditions (cerebral malaria v/s P.falciparum malaria with hypoglycemia) are different. Administration of I.V. quinine further increases the severity of hypoglycemia and facilitates the adverse outcome.

The overall incidence of hypoglycemia in patients with severe falciparum malaria is likely to be high. But the diagnosis in such patients poses obvious difficulties. Changes in level of consciousness or depending coma, are usually attributed to cerebral malaria, and other signs such as sweating and tachycardia are common there were three deaths (37.5% mortality) in cerebral malaria with hypoglycemia group. To conclude that survival probability increases as blood sugar level is raised from hypoglycemia to Euglycemia. Statistically requires a large sample study. The three deaths are because of old age with ARDS, Acute renal failure and severe hepatic involvement respectively.

5% of the patients of vivax malaria showing hypoglycemia but there were no deaths. It may be because of prolonged fasting during high fevers are because of drugs.

Hypoglycemia is an important accompaniment of severe falciparum malaria and has a great influence and ultimate outcome of cerebral malaria.

Early recognition and proper correction may save the life of a person who is in deep coma due to hypoglycemia only, as P. falciparum malaria with hypoglycemia and cerebral malaria are sometimes indistinguishable at the time of admission.

The results of our study are coinciding with the previous studies. It is clear that the blood sugar levels must be measured on admission in all patients, with malaria and regularly thereafter. In the absence of means to measure blood sugar, hypoglycemia should be suspected in any comatose patients with malaria and treated appropriately.

At various levels of health care system, the awareness of hypoglycemia in malaria is low. At peripheral and community health centers the staff should be made aware of the nature and importance of hypoglycemia in malaria and they should be educated to detect and treat hypoglycemia promptly.

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