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"A hospital based study on the value of hemoglobinuria in the diagnosis and outcome in cases of complicated malaria"

Dr. Pradeep Prasad[1], Dr. Sanjay Kumar[2]

1. *Senior Resident, Department of Laboratory Medicine, Rajendra Institute of Medical Sciences, Ranchi.*
2. *Attending Consultant, Department of Critical Care, Medanta Hospital, Ranchi.*

Abstract:

1. *Introduction: Malaria is a global health problem with over 40% of the world's population i.e. more than 3000 million people exposed to varying degrees of malaria risk in some 108 countries. The intravacualr haemolysis can be due to non-immune destruction of parasitized red blood cells in case of high parasitemia or due to immune mediated destruction of parasitized as well as non-parasitized red cells.*
2. *Material and Method: The present study "A hospital based study on the value of hemoglobinuria in the diagnosis and outcome in cases of complicated malaria" was carried out in the patient admitted in the Department of Medicine of Rajendra Institute of Medical Sciences, Ranchi, with diagnosis of P. falciparum malaria suggestive of complicated (severe) form of falciparum malaria according to WHO 2000 criteria.*
3. *Results: Parasite density ranged from 3-18%, and high parasite density > 10% was associated with increased morbidity and mortality in hemoglobinuria patients compared to patients without hemoglobinuria. Overall mortality in complicated malaria was 275%. Out of these deaths, 41.17% was seen in hemoglobinuria patients and 23.80% in patients without hemoglobinuria.*
4. *Conclusion: There is definite correlation between parasitemia and hemoglobinuria.early detection can leads to decreased mortality.*

Key Words: *Malaria; Hemoglobinuria; Parasitemia.*

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I. Introduction

Malaria is a global health problem with over 40% of the world's population i.e. more than 3000 million people exposed to varying degrees of malaria risk in some 108 countries.

As with the continued recent advancement of civilization and achievements in the field of medical sciences disease like AIDS, ischemic heart disease, cerebrovascular accidents, diabetes, mellitus, dyslipidemia but the disease of ancient time malaria still remains most important disease in world and developing countries and is a major cause of mortality and morbidity. It is endemic in 91 countries, mostly in the tropical regions. Nearly 1 million deaths are attributable to malaria each year in these countries. It undermines the health and welfare of families, endangers the survival of children, debilitates the active population and is a major obstacle in socio-economic development.

The origin of the term malaria arose from this fact, **mal** meaning **bad** and **aria** meaning air[1]. For this very reason another name was given to the disease - **paludism, palus** meaning **marsh** in Latin[2]. Evidence for the fact that malaria existed in ancient times, comes from studies of Egyptian mummies.

The specific causative agent of malaria was discovered in the RBC of a patient in the year 1880 by **Charles Alphonse Laveran**, a French army surgeon in Algeria. **Marchiafava** in 1883 used methylene blue to stain malaria parasites[3]. In 1886 **Golgi**, in Italy described the asexual development of the parasite in RBC (erythrocytic schizogony), which thereafter came to be known as Golgi cycle. **Romanowsky** in Russia in 1891 developed a polychrome stain for malaria parasite. Three different species of the parasite causing disease in humans - Plasmodium vivax, Plasmodium malariae and Plasmodium falciparum were identified in Italy between 1886 & 1890. Plasmodium ovale was identified in 1922. In 1887, Ronald Ross in Secunderabad, India found the development of oocysts of malarial parasite on the stomach wail of anopheles mosquito[4]. Bignami, Bastianelli and Grassi in Italy demonstrated the presence of sporozoites in the salivary gland of anopheles mosquito. In 1948 **Short** and **Garnbam** demonstrated the site of exoerythrocytic development in the liver. In the next year they demonstrated the pre-erythrocytic schizogony of Plasmodium falciparum.

Nearly 2 million cases of malaria occur every year in India. The great concern is states like Bihar, Jharkhand, UP, Orissa, Karnataka, Rajashthan, Madhya Pradesh and Pondicherry are recorded high incidence of P. falciparum malaria. There is a rapid rising trend of P. falciparum infection from 21% in 1922 to 41% in 1982

and the ratio of P. falciparum as well and accounts for major cause of death worldwide, 80% of these deaths are caused due to multiple organ failure[5].

In India about 70% of the infections are reported to be due to P. vivax, 25-30% due to P. falciparum and 4-8% due to mixed infection. About 44 million population of tribal areas of Andhra Pradesh, Madhya Pradesh, Gujrat, Maharastra, Bihar, Rajasthan, Orissa and North Eastern states are contributing about 50% of P. falciparum malaria cases of the country[6.] The tribal area of the newly created state of Jharkhand has seen an alarming rise in falciparum malaria cases in the last five years.

Hemoglobinuria: is the presence of free hemoglobin in the urine as a result of intravascular haemolysis. Hemoglobinuria with hematuria occurs as a result of hemoglobinemia (i.e. presence of free hemoglobin in the blood). The hemoglobin released from destroyed red blood cells quickly binds to special plasma globulin called haptoglobin. The haptoglobin binding capacity is exceeded when excessive amount of hemoglobin is released in circulation associated with intravascular haemolysis. The free hemoglobin is readily filtered through glomerulus. Some of the hemoglobin is reabsorbed into the tubular epithelial cells arid remaining unabsorbed hemoglobin is lost in urine causing hemoglobinuria[7,8].

The intravacualr haemolysis can be due to non-immune destruction of parasitized red blood cells in case of high parasitemia or due to immune mediated destruction of parasitized as well as non-parasitized red cells. The changes in red cell antigen structure brought about by parasitic invasion stimulate the production of antibodies against the red cells. This triggers the immune mediated red cell lysis. Sensitivity to quinine may play a role in some patients who have been treated with quinine. The haemolysis can occur so rapidly that heamoglobin may drop significantly within a few hours and it may recur periodically at intervals of hours or days. The patient presents with headache, nausea, vomiting and severe pain in the loin and prostration. Fever upto 39.4°C with rigor is also seen. The urine becomes darker and output slowly drops. Renal failure and peripheral circulatory failure are the usual causes of death in these patients[71]. Similarly the parasite count may not represent the actual parasite load. Renal functions get affected and the urea and creatinine levels rise. There is increase in the levels of unconjugated and conjugated bilirubin as well. Hepatic failure can occur in severely ill patients and is of grave prognosis[9].

Ekvall H et al (2001)[8] studied that Acute haemolysis associated with clinical episodes of high level P. falciparum parasitemia was studied in 20 children from holoendemic area. The change in blood hemoglobin (Hb) concentration ranged from 4 to 6 gm/dl during the 72 hours observation period and was related to parasitemia. Studies between loss of blood Hb, increase in plasma Hb and appearance of Hb in the urine indicated that extravascular clearance of red blood cells was predominant mode of erythrocyte clearance. Most subjects however showed signs of intravascular haemolysis. The plasma Hb was < 1% of blood Hb and hemoglobinuria was detected in 14/20 children but the excretion of hemoglobin in urine was < 0.5% of total Hb loss. Hemoglobinuria was however a marker of severe haemolysis, since maximum blood Hb loss in children without hemoglobinuria was 10 gm/dl.

II. Materials And Methodology

The present study "A hospital based study on the value of hemoglobinuria in the diagnosis and outcome in cases of complicated malaria" was carried out in the patient admitted in the Department of Medicine of Rajendra Institute of Medical Sciences, Ranchi, with diagnosis of P. falciparum malaria suggestive of complicated (severe) form of falciparum malaria according to WHO criteria.

The following definition of complicated falciparum malaria proposed by WH0[10]:

Severe falciparum malaria is defined as:

(1) One or more of the defining criteria below

(2) Asexual parasitemia with Plasmodium falciparum (although smear-negative cerebral malaria may occur)

Defining Criteria	**Finding**
Cerebral malaria (unrousable coma)	Unrousable coma not attributable to any other cause in a patient with falciparum malaria. Coma should persist at least 30 minutes after a generalized convulsion to make the distinction from transient post ictal coma.
Severe normocytic anaemia	Normocytic anaemia with haematocrit < 15% or haemoglobin < 5 gm/dl in the presence of parasitemia more than 100 parasites per µ1. If microcytic indices seen need to consider iron deficiency anaemia, thalassemia and hemoglobinopathy.
Renal failure	Urine output <400 ml in 24 hours in adults or 12 ml per Kg in children failing to improve after rehydration and with serum creatinine more than 265 µ mol/l (3 mg/dl).
Pulmonary edema ARDS	Noncardiogenic pulmonary edema, often aggravated by overhydration.
Hypoglycemia	Whole blood glucose <2.2 mmol/l (<40 mg/dl).
Circulatory collapse shock	Hypotension (systolic blood pressure <50 mm Hg in children 1-5 years old; <70 mm Hg in adult) with cold clammy skin or a core to skin temperature difference more than 10° C.
Spontaneous bleeding DIC	Spontaneous bleeding from gums, nose, GI tract or other sites with laboratory evidence of DIC.
Repeated generalized seizures	More than 2 observed seizures (> = 3) within 24 hours despite cooling.

Acedemia or Acidosis	Arterial pH < 7.25, plasma bicarbonate < 15 mmol/1.
Malarial hemoglobinuria	Need to exclude hemoglobinuria due to antimalarial medications and to G-6PD deficiency.

Additional criteria	**Findings**
Impaired consciousness but rousable	Impaired consciousness less marked than unarousable coma can localize a painful stimulus.
Prostration and extreme weakness	Patient unable to sit or walk with no other obvious neurological explanation
Hyperparasitemia	Very high parasite densities are associated with increased risk of severe disease but is affected by immune status (more than 5% parasitemia in non-immune is serious but may be well tolerated in semi-immune children); >5000 per µ l.
Jaundice	Total bilirubin >50 µ mol/l (>3 mg/dl).
Hyperpyresia	Rectal temperature > 40^0 C.
Post-mortem evidence of severe malaria	Neuropathologic evidence of venules and capillaries packed with erythrocytes containing malarial parasites.

Laboratory Diagnosis of Hemoglobinuria
Benzidine test
Requirements
• Test tube
• Graduated pipettes - 5 ml
• Pasture pipettes
• Benzidine powder (3 3' 5 5' tetramethyl benzidine)
• Glacial acetic acid
• Hydrogen peroxide (30% v/v)
Procedure
• Place pinch of benzidine powder in a test tube
• Add 2 to 3 drops of glacial acetic acid and mix well
• Add about 2 ml of hydrogen peroxide solution and mix well Transfer one ml of supernatant to a test labelled as T
• Add 0.5 ml of urine and mix
• Observe the colour mixture after 5 minutes.
Observation
No change of colour — Absence of hemoglobin in urine
Colour changes — Presence of hemoglobin in urine

Colour	Report (Benzidine test)
Paint green	Trace
Green	+
Greenish blue	++
Blue	+++
Deep blue	++++

III. Results

Table – I: Age distribution of hemoglobinuria cases among complicated malaria cases under study

Age group (Years)	No. of cases (n = 80)	Cases with haemoglobinuria (n = 17)	Percentage of haemoglobinuria cases in given age group
< 20	12(15%)	2(11.76%)	16.6
20-40	43(53.75%)	11(64.70%)	25.6
41-60	19(23.75%)	3(17.64%)	15.8
> 60	6(4-7.5%)	1(5%)	

Maximum numbers of complicated cases of P. falciparum malaria cases i.e. 43 (53.75%) were seen in age group 20-40 years, among which hemoglobinuria was commonly seen in same age group i.e. 11 cases (25.6%).

Table – II: Rural and Urban distribution of hemoglobinuria cases under study

	Total No. of cases (n=80)	Number of haemoglobinuria cases (n=17)
Urban	22(27.5%)	1(5.88%)
Rural	58(72.5%)	16(94.11%)

A majority of patients suffering from complicated malaria were from the rural areas (72.5%). Hemoglobinuria was also common among rural areas amounting to 94.11%. Maximum numbers of hemoglobinuria cases were from certain pockets namely Silli, Bundu, Ormanjhi, Sonahatu, Tatisilwai, Gumla and Lohardaga district.

Table – III: Distribution of hemoglobinuria cases in complicated malaria among tribal and non-tribal

	Total No. of cases (n=80)	Number of haemoglobinuria cases (n=17)
Tribal	57(71.25%)	13(76.47%)
Non-tribal	23(28.75%)	4(23.53%)

In comparison to the population of tribal in Chotanagpur area, which is in the range of 30-35%, the incidence of complicated malaria cases was (71.25%) which was associated with hemoglobinuria cases (76.47%), incidence of which was higher in tribal population.

Table – IV: Distribution of hemoglobinuria cases in complicated malaria in relation to the level of parasitaemia in the study

Parasitaemia (%)	No. of complicated cases (n=80)	No. of haemoglobinuria cases (n=17)
Up to 5	25(43.75%)	3(17.64%)
6-10	23(28.75%)	4(23.52%)
Above 10	22(27.50%)	10(58.82%)

As in the present study of 17 cases of hemoglobinuria among complicated malaria cases majority of the patients (58.82%) has parasite density over 10%. In the remaining 7 cases of hemoglobinuria 4 cases (23.52%) were associated with parasite density 6 to 10% and remaining 3 cases (17.64%) were associated with parasite density upto 5%.

Table – V: Different clinical presentation of hemoglobinuria cases in patients with complicated malaria cases under study

Clinical presentation	No. of complicated case(n=80)	No. of hemoglobinuria cases (n=17)
Fever, chills and rigor	80(100%)	17(100%)
Headache	80(100%)	17(100%)
Coma	41(51.25%)	15(88.23%)
Convulsion	19(23.75%)	7(41.17%)
Altered sensorium	17(21.25%)	10(58.82%)
Jaundice	33(41.25%)	11(64.70%)
Oliguria/Renal failure	35(43.75%)	10(58.82%)
Anemia(severe)	25(31.25%)	11(64.70%)
Hypoglycemia	9(11.25%)	3(17.64%)
Shock	13(17.5%)	2(11.76%)
Pulmonary edema	6(7.5%)	3(17.64%)
Hemoglobinuria	17(21.25%)	17(100%)
Hepatomegaly	17(21.25%)	2(11.76%)
Splenomegaly	25(31.25%)	3(17.64%)

Fever with chill and rigor along with headache was the most common presentation. As this study included cases of complicated malaria, a sizeable number of cases presented with cerebral malaria (41 cases out of 80 cases i.e. 51.25%) associated with coma, convulsion and altered sensorium. Jaundice (41.25%), oliguria (43.75%), severe anaemia (3 1.25%), shock (17.5%), pulmonary oedema (7.5%) and hemaglobinuria (21.25%) were seen as complication in present study.

Among hemoglobinuria cases incidence of cerebral malaria was 88.23%, jaundice 64.7%, renal failure 58.82%, anemia 64.7%, fever with chills and rigor and headache 100% each.

Table – VI: Outcome of hemoglobinuria cases in patients of complicated malaria

	Total No. of cases	Cured	Death
Hemoglobinuria cases	17	10 (58.82%)	7 (41.17%)
Cases without hemoglobinuria	63	48 (76.20%)	15 (23.80%)

In the present series among 17 cases of hemoglobinuria 10 (58.82%) were cured but 7 cases (41.17%) died compared to cases without hemoglobinuria in complicated malaria in which 48 cases (76.20%) were cured and 15 cases (23.80%) died. But overall mortality was 22 cases (27.50%).

Table – VII: Relationship between level of parasitaemia and the outcome in hemoglobinuria cases compared to complicated malaria

Parasitaemia (%)	No. of hemoglobinuria cases (n=17)		No. of complicated malaria cases without hemoglobinuria (n=63)	
	Recovery	Death	Recovery	Death
Less than 5	1	0	21	2
5-10	5	1	24	3
> 10	4	6	3	10

In the above table 10 cases of hemoglobinuria with parasite density above 10%, death occurred in 6 patients and recovery in 4 patients. Remaining 6 cases in which parasite density ranging 5 to 10%, recovery was seen in 5 cases and death in 1 case. One case was associated with parasite density less than 5% which recovered. In cases without hemoglobinuria cases maximum death was also seen in patients with parasite density more than 10% (10 deaths and 3 recovery). Mortalites is a Parasitamia.

IV. Discussion

Majority of cases around two third were seen in age group 20-60 years, of which around 60% of cases belong to younger age group 20-40 years. Hemoglobinuria as a complication and marker for diagnosis of complicated cases were uniformly present in all age groups, in range of 17-25%. Highest numbers of cases were present in age group 20-40 years i.e. 26%. The reason for higher incidence was because this age group represents the most active group of the society Young people of this age group are frequently engage in outdoor activities like working in agricultural farms, migration of labour from non-endemic to endemic area, working in field or places having stagnant water like ditches, ponds, irrigation channels, forestation of shrubs, which are the breeding places causing adaptation of mosquitoes. This increases the chances of mosquito bite.

Table – II tries to focus on rural and urban distribution of complicated malaria and its association with hemoglobinuria. In this study, needless to say that of Jharkhand and adjoining areas are largely rural forest cover. Majority of cases come from rural areas {72%} compared to urban areas {27%} due to poverty, lack of education and unhygienic condition. Agriculture practice is most common occupation in rural areas. The infrequent use of mosquito nets and sleeping outdoor increases chance of mosquito bite Treatment by untrained local quacks often compounds the situation.

In the present study incidence of complicated malaria with hemoglobinuria was seen in parasite density varying from< 5% to > 10%. But incidence of hemoglobinuria were mostly seen in patients with parasite density >10%. Hemoglobinuria is due to massive intravascular hemolysis causing by non-immune and immune mediated destruction of parasitized RBC due to high parasitemia causing change in RBC antigen structure brought about by parasitic invasion stimulating antibody production against red cell causing red cell lysis leading to black water fever.

The patients presented with the C/F in complicated malaria cases with and without hemoglobinuria which was associated with various presentation like cerebral malaria 5l.25%, jaundice 41.25%, renal failure 43.75%, severe anaemia 31 .25%, fever with chills and headache 100%, hemoglobinurea 21.25%, pulmonary edema 7.5% shock 17.5% convulsion 23.75%. The high incidence of complication in hemoglobinurea patient may be attributed to degree of parasitemia.

The mortality in patient with hemoglobinuria was 7(41 .17%) compared to patient of complicated malaria without hemoglobinuria 15 (23.80%) The reason for high mortality in hemoglobinuria cases may be high degree of parasitemia >10%. Causing complication and multiorgan failure. Further delay in diagnosis and treatment may be an additional factor. Out of 17 cases of hemoglobinurea, 10 cases of hemoglobinuria (58.82) were having parasite density > 10%, 6 cases (35.29) with parasite density 5-10%. Majority of death occuread in patient with high parasite count.

V. Conclusion

Severe complicated malaria is an important cause of mortality in P. falciparum infection. In this study 80 cases of complicated malaria according to World Health Organization, 2000 criteria was studied and following findings emerged.

Most of the complicated malaria cases were seen in the younger age group upto 40 years (68.75%). Majority of cases of complicated malaria came from rural areas (72.5%) and from the low socioeconomic group (75%). Fever with chills & rigor with headache was the most common presentation (100%).

Parasite density ranged from 3-18%, and high parasite density > 10% was associated with increased morbidity and mortality in hemoglobinuria patients compared to patients without hemoglobinuria. In the present study parasite density was directly proportional to the severity of the illness.

Overall mortality in complicated malaria was 275%. Out of these deaths, 41.17% was seen in hemoglobinuria patients and 23.80% in patients without hemoglobinuria. Renal failure was seen in 10 cases (58.82%) with 5 deaths (50%) in hemoglobinuria cases compared to patients without hemoglobinuria in which 24 cases (38.10%) with death in 7 cases (29. 16%) occurred.

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