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A Study of Clinical Profile of Severe Falciparum Malaria in Tertiary Care Hospital, Gujarat

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Abstract

Background: Among the four different protozoan parasites to genus plasmodium, P. Falciparum causes an acute and potentially lethal illness and is known to cause atypical manifestations, high mortality and drug resistance, particularly in tropic areas.

Objectives: To study clinical profile of severe falciparum malaria.

Materials and methods: This is a cross sectional observation study conducted at tertiary care hospital to know how many patient positive for p. falciparum has suffered with severe symptoms. In these study, clinical examination and investigation like CBC, peripheral smear, ESR, LFT, X ray Chest and some special investigations like CSF analysis, CT scan of brain, etc was done.

Results: Out of 50 patients, 60% were male and 40 % were female. Commonest complication in the present study was anemia (48%), but severe anemia (< 5gm%) occurred in 5(10%) of patients. Other complications seen were jaundice (26%), bleeding tendency (24%), neurological involvement (22%), hypoglycemia (18%), hypotension (14%) septicemia (12%) ARDS (5%),
pancytopenia (4%).

Conclusion: P. falciparum malaria continues to produce life threatening complications with great morbidity and mortality.

Keywords: Cerebral malaria, Hyper parasitemia, DIC, Hemoglobinuria

Introduction

Malaria or ague is one of the oldest recorded diseases in the world. In 18TH century, people of Italy believed that the intermittent fever with rigors was due to poisonous or bad air- “malaria”, from which the name Malaria was derived. In Europe, seasonal periodic fever was common in marshy areas, and was referred to as “paludial” (L.palus-marshy ground.)

Malarial parasites have been with us since the dawn of time. They probably originated in Africa (along with mankind). Fossils of mosquitoes up to 30 million years old show that the vector for malaria was present well before the earliest history. The Plasmodium parasites are highly specific, with the man as the only vertebrate host and Anopheles mosquito as the vectors.

Amongst the four different protozoan parasites to genus plasmodium, P. Falciparum causes an acute and potentially lethal illness (so malignant Malaria in older terminology) and is known for atypical manifestations, severity, high mortality and drug resistance, particularly in tropics. There has been an upward trend in the past few years for reporting various severe manifestations of Falciparum malaria,

as well as the incidence of drug resistance to standard chemotherapeutic agents.

The present study was conducted to find out the various severe manifestations of Falciparum malaria, with view to understand this important disease.

Aims And Objectives:

1. To Study the clinical profile of severe falciparum malaria.

2. To study the response of various anti-malarial drugs used in treatment of severe p. Falciparum malaria.

Materials And Methods: A cross sectional observation study was conducted with 50 patients at tertiary care hospital, gujarat from April 2020 to April 2022. Patients were selected on basis of inclusion and exclusion criteria and predesigned proforma for data collection.

Inclusion Criteria:

1. Patients in whom presence of asexual P. Falciparum malaria parasites seen on peripheral smear.
2. Patients having P. Falciparum malaria and showing severe manifestation of disease.
3. Patients of P. Falciparum malaria who had given written informed consent to be part of this study.

Exclusion Criteria:

1. Patients with positive peripheral smear examination showing ring forms (Trophozoites) of P. Falciparum malaria but without any complications.
2. Patients who had not given written informed consent for the study.

Sample Size Calculation:

Sample size = (Z2pq)/d2

Where n = sample size, z = the standard normal deviate, which is 1.96 at 95% confidence interval, p = prevalence in the population of the factor under study.

Here we take p =12% = 0.12 (from census data), Hence q = 1 – p = 0.88 d = absolute precision = 9

Then using formula n = 51.6, so we have to take at least 50 patients.

Methodology:

All patients underwent detailed laboratory investigations which compromised of Peripheral smear, Hemoglobin percentage, Total WBC count, ESR, P/s for malaria parasite, Random blood sugar, Urine examination, Liver function test, S. Widal, X-ray chest, ECG (electrocardiogram), BT, CT, Platelet count.

Other specific investigations done when indicated were CSF analysis, CT Scan of brain, Urine hemoglobinuria, Australia antigen test (HbsAg). Blood culture in all patients with positive Widal test.

Manifestations of Severe Falciparum Malaria	
SIGNS	MANIFESTATIONS
MAJOR	-
UNAROUSABLE COMA/CEREBRAL MALARIA	FAILURE TO LOCALIZE OR RESPOND APPROPRIATELY TO NOXIOUS STIMULI; COMA PERSISTING FOR >30 MIN AFTER GENERALIZED CONVULSION
ACIDEMIA /ACIDOSIS	ARTERIAL PH <7.25 OR PLASMA BICARBONATE LEVEL OF <15 MMOL/L; VENOUS LACTATE LEVEL OF >5 MMOL/L; MANIFESTS AS LABORED DEEP BREATHING, OFTEN TERMED "RESPIRATORY DISTRESS"

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SEVERE NORMOCHROMIC, NORMOCYTIC ANEMIA	HEMATOCRIT OF <15% OR HEMOGLOBIN LEVEL OF -£50 G/L (<5 G/DL) WITH PARASITEMIA LEVEL OF >100,000/L
RENAL FAILURE	URINE OUTPUT (24 H) OF <400 ML IN ADULTS OR <12 ML/KG IN CHILDREN; NO IMPROVEMENT WITH REHYDRATION; SERUM CREATININE LEVEL OF >265 MOL/L (>3.0 MG/DL)
PULMONARY EDEMA/ADULT RESPIRATORY DISTRESS SYNDROME	NONCARDIOGENIC PULMONARY EDEMA, OFTEN AGGRAVATED BY OVER HYDRATION
HYPOGLYCEMIA	PLASMA GLUCOSE LEVEL OF <2.2 MMOL/L (<40 MG/DL)
HYPOTENSION/SHOCK	SYSTOLIC BLOOD PRESSURE OF <50 MMHG IN CHILDREN 1- 5 YEARS OR <80 MMHG IN ADULTS; CORE/SKIN TEMPERATURE DIFFERENCE OF >10°C; CAPILLARY REFILL >2 S
BLEEDING/DISSEMINATED INTRAVASCULAR COAGULATION	SIGNIFICANT BLEEDING AND HEMORRHAGE FROM THE GUMS, NOSE, AND GASTROINTESTINAL TRACT AND/OR
	EVIDENCE OF DISSEMINATED INTRAVASCULAR COAGULATION
CONVULSIONS	MORE THAN TWO GENERALIZED SEIZURES IN 24 H; SIGNS OF CONTINUED SEIZURE ACTIVITY SOMETIMES SUBTLE (E.G., TONIC-CLONIC EYE MOVEMENTS WITHOUT LIMB OR FACE MOVEMENT)
HAEMOGLOBINURIA	MACROSCOPIC BLACK, BROWN, OR RED URINE; NOT ASSOCIATED WITH EFFECTS OF OXIDANT DRUGS AND RED BLOOD CELL ENZYME DEFECTS (SUCH AS G6PD DEFICIENCY)
OTHER	
IMPAIRED CONSCIOUSNESS/AROUSABLE	UNABLE TO SIT OR STAND WITHOUT SUPPORT
EXTREME WEAKNESS	PROSTRATION; INABILITY TO SIT UNAIDED

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HYPERPARASITEMIA	PARASITEMIA LEVEL OF >5% IN NONIMMUNE PATIENTS (>20% IN ANY PATIENT)
JAUNDICE	SERUM BILIRUBIN LEVEL OF >50 MMOL/L (>3.0 MG/DL) IF COMBINED WITH OTHER EVIDENCE OF VITAL-ORGAN DYSFUNCTION

"HEMOGLOBINURIA MAY OCCUR IN UNCOMPLICATED MALARIA.

IN A CHILD WHO IS NORMALLY ABLE TO SIT.

NOTE: G6PD, GLUCOSE-6-PHOSPHATE DEHYDROGENASE.

Results:

All age groups are affected by P. falciparum malaria. The present study shows that maximum numbers of patients were in age group of 21-30 years that is 15(30%) followed by 41-50 years in which there are 11(22%) patients. The reason for high prevalence of these age groups could be working group in these age groups going outside their home for earning, their work places and migration to different areas for work. Male predominance is probably because of clothing style in India and outdoor lifestyle.

Malaria is more common in rural areas because of poor vector control and poor hygienic conditions. Poor availability of health resources is also responsible for more severe malaria in rural areas.

Most of patients had intermittent pattern of fever (84%), some of the patients had low grade fever (2%) overlapped by spikes of high-grade intermittent fever pattern.

High grade fever is a common feature of severe P. falciparum malaria. But clinical tertian (malignant tertian) fever is seen only if patients were untreated. But commonly irregular spiking fever corresponding to schizogony is more usual. High grade fever is sometimes associated with behavioral changes.

Present study shows that fever, headache, vomiting, icterus, body ache, and altered sensorium were common presenting symptoms. Most common presenting symptom was fever and least common presenting symptom was diarrhea.

The common signs were splenomegaly (66%), followed by anemia (48%), hepatomegaly (34%) and icterus (22%).

In present study splenomegaly was present in (66%) case, anemia in (48%) of cases, hepatomegaly in (34%) of patients, icterus in (22%) of patients, altered sensorium was observed in (22%) of patients.

In the present study 100 patients had pyrexia out of which 78% had temperature in the range of 100-102. Hyperpyrexia was not recorded in any patient. Lowest temperature was 99 F and the highest temperature recorded was 103 F.

Severe anemia, acute renal failure, jaundice and neurological involvement were the commonest complications which were also common in other studies. In our study severe anemia was present in 5 (10%) patients, 12(32%) had acute renal failure, 13(26%) had jaundice and 11(22%) had neurological involvement. Septicemia was present in 6(12%) of patients and 6(12%)) had septicemia.

In our study 11 out of 50 (22%) patients with P. falciparum malaria had neurological involvement.

Altered sensorium is the most common presentation in patients with cerebral malaria. In present series 6/11 (54.5%) patients had varying level of altered sensorium. Out of that 1(20%) were deeply unconscious, 2(40%) were stuporous and 2(40%) were drowsy on admission.

Convulsions in P. falciparum malaria are usually generalized but Jacksonian type or persistent focal seizures are also observed. In present study 4 (36.36 %) patients had convulsion. Psychiatric

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manifestations like transient paranoid psychosis, delirium etc. may be presenting feature in patients with acute P. falciparum malaria especially if there is high grade fever and complication of phenothiazines or other drugs. No patient in study had psychiatric manifestations.

In WHO bulletin various rare presentations of cerebral malaria have been described, which include cranial nerve lesions, extra pyramidal symptoms, tremors, polyneuropathy, mononeuritis multiplex, Guillain Barre syndrome and greatly prolonged coma.

In present study 1 patient is noted to have such rare manifestation in form of extra-pyramidal symptoms. 16(32%) patients are noted to have impaired renal function in the present study.

In this group with altered renal function, anemia was the major associated complication (62.5%) patients and hypotension (45%) was second most common complication.

In our study, mean blood urea value of the 16 patients with altered renal functions was 121 mg%. Most of patients (62.5%) had the blood urea level between 101-200. Most of the others (37.5%) had blood urea level below 100 mgm/dl while a none had blood urea more than 201 mgm/dl. The mean Creatinine value in 16 patients with altered RFT is 3.3 mg/dl. In the present study most of the patients with altered S Creatinine 11(68.75%) fall in the range of 1.5 to 3.0 mg/dl. In the present study most of the patients with altered renal function had S. Potassium level in the range of 3.5 to 5 mEq/1.

Hematuria was noted in 4 & proteinuria in 12 patients. Urinary abnormalities are attributable to glomerulonephritis due to immunological reaction to parasites. Proteinuria is less than 1 gm in 24 hours and disappears as fever subsides or within 2-3 wks. 13(26%) patients in the present study had hyperbilirubinemia. The mean bilirubin in 13 patients is 4.2 mg/dl. Majority of the patients that is 9/13 (69.2%) had bilirubin in the range of 2-10 mg/dl. Out of 13/50 patients with jaundice, 8(61.53%) of the patients had SGPT >100 IU/L and 8(61.5%) of the patients had SGOT>100 IU/L. This data suggests in our study the patients with jaundice and elevated S. Bilirubin level had SGOT and SGPT level above 100 IU/L.

Most of the patients 24 (48%) had blood sugar in the range of 60-l00 mg/dl in the present study. According to WHO guideline hypoglycemia less than 40mg/dl with symptoms of hypoglycemia. We had 1 patient with blood sugar <40 mg/dl with typical signs and symptoms of hypoglycemia. We had 2 patients with typical signs and symptoms of hypoglycemia and responded to intravenous glucose but their blood sugar level was in the range of 40-60 mg/dl.

Present study shows incidence of anemia in 48% of patients and 10% of the patients had severe anemia. It is evident that anemia is an important contributary factor for cause effect relationship of malaria. Severe anemia predisposes to severe malaria and high mortality. One patients who expired in the study had moderate to severe anemia.

Leukocyte count is usually normal in acute falciparum malaria however leukocytosis can occur with secondary bacterial infection and pernicious syndrome. Peripheral leukocytosis is a bad prognostic sign. Majority of the patients 29(58%) in the present study had normal leukocyte count. 9(18%) had leukocytosis, mostly associated with secondary bacterial infection. Leukopenia is infrequently associated with acute P falciparum malaria was noted in 4(8%) of the patients.

Thrombocytopenia is a common presentation of P falciparum malaria with spontaneous recovery on treatment. About 21(42%) of the patients had thrombocytopenia in the present study with normal hemostasis in most cases. Lowest platelet count recorded was 5,000/cmm. The mean platelet count was 1,10,000/cmm.

In the present study one patient had jaundice, while one had bleeding P/V.

Majority of the patients were given Artesunate as the first line treatment in the present study. Total 33(66%) of patients were given Artesunate. In most patients Artesunate was given by IV route, followed by tablets as soon as the patient could take drugs orally and was afebrile. Main side effects were gastrointestinal. Total 17(34%) of the patients were given Quinine. The drug was well tolerated in most of the patients and most common side effect was gastrointestinal and one patient developed hypotension following quinine administration and was switched over to artesunate.

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Out of 100 patients studied 2(4%) expired in the hospital. One patient died of cerebral malaria who also developed simultaneous ARDS. (Acute Respiratory Distress Syndrome). One patient had severe anemia with jaundice also had associated acute renal failure along with anemia and jaundice. P. falciparum malaria with cerebral involvement is associated with high mortality and when complications are multiple the mortality rates are further aggravated.

Table 1: Incidence of complications

COMPLICATIONS	PRESENT STUDY n=50	KATYAL et al n=66	BANZAL et al n=256
SEVERE ANAEMIA	5(10%)	25(37.9%)	97(39.4%)
ACUTE RENAL FAILURE	16(32%)	9(13.6%)	15(6.1%)
NEUROLOGICAL INVOLVEMENT	11(22%)	26(39.4%)	64(26%)
JAUNDICE	13(26%)	34(51.4%)	58(23.5%)
PANCYTOPAENIA	2(4%)	4(6.4%)	NR
ARDS	3(6%)	2(3%)	5(1.6%)
HYPOGLYCEMIA	9(18%)	4(6%)	5(1.6%)
BLEEDING TENDENCIES	12(24%)	NR	13(5.2%)
SEPTICEMIA	6(12%)	2(3%)	NR
HYPOTENSION	7(14%)	NR	NR

Figure 1: Graph of percentage of complications

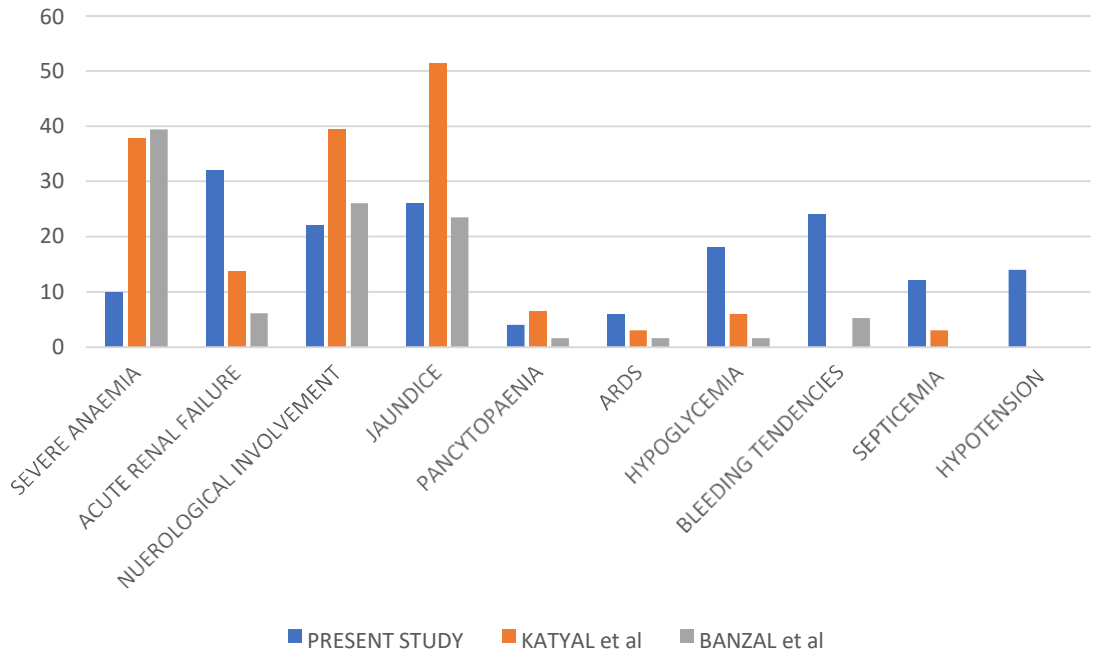

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Table 2: Hematological parameters

HEMATOLOGICAL PARAMETERS	PRESENT STUDY n=50	SHARMA et al n=30	KATYAL et al n=66
Hemoglobin			
> 10	26 (52%)	4 (13.3%)	10 (15.5%)
5-10	19 (38%)	23 (76.7%)	31 (46.9%)
< 5	5 (10%)	3 (10%)	25 (37.9%)
Total Leukocyte Count			
> 11,000	9 (18%)	4 (13.3%)	0
4,000 - 11,000	29 (58%)	24 (80%)	57 (86.4%)
< 4,000	4(8%)	2 (6.7%)	9 (13.9%)
Platelet Count			
>1,50,000	11 (22%)	3 (10%)	54 (81.8%)
50,000-1,50,000	21 (42%)	26 (86.67%)	12 (18.2%)
< 50,000	18 (36%)	1 (3.33%)	0

Discussion:

50 hospitalized patients with P. falciparum malaria (positive peripheral smear of parasite) with various severe manifestations of malaria were studied.

Out of 50 patients, 60% were male and 40 % were female. Male female ratio is 1.5.1. However, 66% patients were young below 40 years.

All patients had fever. However, 84% of the patients had fever with intermittent pattern which was associated with chills & rigors and of 2- 10 days in duration.

The presenting symptoms were fever (100%), vomiting (56%), headache (46%), oliguria (32%),

body ache (26%), altered sensorium (22%), bleeding tendency (20%), dyspnea (18%), epigastric

pain (16%), convulsions (16%), icterus (12%), diarrhea (8%).

Physical signs commonly present were splenomegaly (66%), anemia (48%), hepatomegaly (34%), icterus (22%), altered sensorium (22%), and hypotension (14%).

39 (78%) of the patients had fever between 101° F-1020 F but no patient had hyperpyrexia i.e. (>104°F).

Commonest complication in the present study was anemia (48%), but severe anemia (< 5gm%) occurred in 5(10%) of patients. Other complications seen were jaundice (26%), bleeding tendency (24%), neurological involvement (22%), hypoglycemia (18%), hypotension (14%) septicemia

(12%) ARDS (5%), pancytopenia (4%).

Out of 50 patients 11 had neurological involvement, out of which 6(54.5%) had altered sensorium, 4(36.36%) had convulsions, 1(9%) had extra pyramidal symptoms.

Altered renal function was found in 16(32%) patients. Serum creatinine >3mg/dl was found in 5(10%) patients. Out of them blood urea>100 mg/dl was found in 10(20%) patients. Hyperkalemia (Serum potassium >5mEq/l) was found in 2(4%) patients. Apart from antimalarial drugs 1(2%) patients required dialysis at our AKD department.

Liver functions were altered in 13(26%) of patients. Out of them 9(69.2%) patients had serum bilirubin in

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the range of 2-10 mg%, and 8(61.53%) had SGPT>100 IU/L while 8(61.5%) had SGOT>100IU/L. One patient developed hepatorenal shut down and expired.

Anemia was found in 24(48%) of patients, out of them severe anemia (Hb< 5gm %) was found in 5(10%) patients. Total leukocyte count was in the normal range that is between 4,000-11,000 in 29(58%) patients, leukocytosis in 9(18%) patients, leucopoenia in 4(8%) of the patients and thrombocytopenia (platelet count < 50,000) were noted in 18(36%) of the patients.

3 patients had DIC while bleeding tendency was found in 12 patients.

Quinine or Artesunate was given as the first line of treatment. Artesunate was given in 66%, Quinine in 34%, while 32% patients were given Quinine with Doxycycline. Patients were given antibiotics; blood transfusion, dialysis and other supportive treatment were given when needed.

Mortality rate was 4% (2 out of 50) in the present study 1 patient had cerebral malaria with ARDS. 1 patient had severe anemia with jaundice which also had ARF with hypotension and pulmonary edema.

Mortality in patients who received Quinine and Artesunate could be due to late presentation or late referral (3 to 4days), older age, multiple complications, severe and mixed infections and preexisting comorbidities. Quinine and Artesunate proved to be effective chemotherapeutic agents in our study and were well tolerated.

Conclusion:

The diagnosis of malaria requires a high index of suspicion.

Definitive diagnosis of malaria requires direct observation of malarial parasite in peripheral blood smears. P. falciparum malaria continues to produce life threatening complications with great morbidity and mortality. Timely antimalarial treatments like Artesunate and Quinine are very effective in the management of severe P falciparum malaria along with therapies like dialysis, blood transfusion, exchange transfusion, antibiotics with intravenous fluid therapy.

Timely antimalarial therapy can effectively reduce development of complications and mortality. Mortality is considerable in patients with severe P falciparum malaria: the important causes being cerebral malaria, severe anemia, renal failure, hepatic failure, ARDS, DIC, hyper parasitaemia, etc.

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