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Clinical profile of patients with severe falciparum malaria

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Abstract
Initially, the host responds to plasmodial infection by activating nonspecific defence mechanisms. Splenic immunologic and filtrative clearance functions are augmented in malaria. Nonspecific host defence mechanisms stop the infection's expansion, and the subsequent specific immune response controls the infection. Eventually, exposure to sufficient strains confers protection from high-level parasitemia and disease but not from infection. As a result of this state of infection without illness (premunition), asymptomatic parasitemia is common among adults and older children living in regions with stable and intense transmission. This study was conducted among adult patients of falciparum malaria. All Adults patients (>14 yrs.) with positive asexual forms of malaria in thick smear, thin smear or positive QBC/ICT test admitted to the hospital were included in the study. Fever was the most common symptom, present in 96.6% of the patients. Other symptoms were vomiting (60%), headache (66.6%), weakness (fatigue) 38.3%, Hepatomegaly and spleenomegaly was present 16.6% and 26.6% respectively.

Keywords: plasmodial infection, severe falciparum malaria, spleenomegaly

Introduction
At present, about 109 countries in the world are considered endemic for malaria. In 2008, there were an estimated 243 million cases of malaria worldwide. The vast majority of cases were in the African Region (85%), followed by the South-East Asia (10%) and Eastern Mediterranean Regions (4%). Malaria accounted for an estimated 863,000 deaths in 2008, of which 89% were in the African Region, followed by the Eastern Mediterranean (6%) and the South- East Asia Regions (5%). Over half of the cases in Africa were in Nigeria, Democratic Republic of the Congo, Ethiopia, United Republic of Tanzania, and Kenya. Outside the African region, 80 per cent cases were in India, Sudan, Myanmar, Bangladesh, Indonesia, Papua New Guinea, and Pakistan. Extensive eradication programs at national levels with assistance from the World Health Organization have met with partial success [1].

When the hepatic meronts (schizonts) rupture, they liberate approximately 10-i 06 merozoites into the circulation (i.e. the product of 5-100 successful sporozoites). These invade passing red cells immediately. In non-immune subjects the multiplication rate in P. falciparum often exceeds 10 per cycle (i.e. >50% efficiency) and may reach 20-fold per cycle during the subsequent expanding phase of the infection. For the first few cycles, the host is unaware of the infection. On average, parasites are detectable in the blood by microscopy on the 11th day after sporozoite inoculation. At this stage, the host may still feel well, or may complain of vague non-specific symptoms of malaise, headache, myalgia, weakness or anorexia. On average, the fever begins 2 days later. The rise in parasite count is logarithmic initially, but in most cases the parasite expansion terminates abruptly to limit the infection at a parasite density of 104-105/pL. Only P. falciparum has the capacity for untrammeled multiplication. Several factors limit parasite multiplication. The host mobilizes specific and non-specific immune defences (particularly in the spleen). The parasite schizonts are damaged by high fevers. The availability of suitable red cells is exhausted [2, 3].

Thus, the untreated infection increases exponentially, then the rate of expansion decelerates rapidly, parasitemia fluctuates, settles around a plateau, then declines and continues for several weeks or months at low levels before finally being eliminated. Although natural infections often contain two or more genetically different parasite strains, development tends to be relatively synchronous from the outset. Temperature 4000 damage mature parasites and further synchronizes parasite cycle. This degree of synchronization is associated with fever spikes and rigors (the 'paroxysm'), and is more likely in P. vivax, P. ovale and P. malariae infections. Although one 'brood' predominates, in P. falciparum there is often at least one minor 'brood' or subpopulation cycling 24 h out of phase with the major brood [4].

Malaria is readily diagnosed from the blood film stained with a Romanowsky dye. In the benign malarias (where sequestration is considered not to occur), the number of parasites in the body may be estimated simply by multiplying the parasitemia by the estimated blood volume. In P. falciparum the microscopist can see only the first third of the asexual life cycle. In the second two-thirds the parasitized cells are sequestered. As a consequence there may be large discrepancies between the number of parasites in the peripheral (circulating) blood and the number of parasites in the body (the parasite burden). The clue to this apparent discrepancy lies in the immune status of the host and in the stage of development of parasites on the peripheral blood smear. A predominance of more mature parasites on the blood film suggests a much greater sequestered parasite biomass, and it carries a worse prognosis than a predominance of younger forms. The presence of intra neutrophilic phagocytised malaria pigment (in more than 5% of neutrophils) is also a valuable prognostic index. Measurement

of proteins released by the parasite, such as Pf HRP2 in plasma, provides a good method of assessing this hidden pathogenic sequestered biomass [5].

Initially, the host responds to plasmodial infection by activating nonspecific defence mechanisms. Splenic immunologic and filtrative clearance functions are augmented in malaria. Nonspecific host defence mechanisms stop the infection's expansion, and the subsequent specific immune response controls the infection. Eventually, exposure to sufficient strains confers protection from high-level parasitemia and disease but not from infection. As a result of this state of infection without illness (premunition), asymptomatic parasitemia is common among adults and older children living in regions with stable and intense transmission. Immunity is mainly specific for both the species and the strain of infecting malarial parasite. Both humoral immunity and cellular immunity are necessary for protection, but the mechanisms of each are incompletely understood. Immune individuals have a polyclonal increase in serum levels of 1gM, lgG, and IgA, although much of this antibody is unrelated to protection. Antibodies to a variety of parasitic antigens presumably act in concert to limit in vivo replication of the parasite. In the case of falciparum malaria, the most important of these antigens is the surface adhesion-the variant protein PfEMP1. Passively transferred lgG from immune adults has been shown to reduce levels of parasitemia in children, passive transfer of maternal antibody contributes to the relative (but not complete) protection of infants from severe malaria in the first months of life. This complex immunity to disease declines when a person lives outside an endemic area for several months or longer [6].

Several factors retard the development of cellular immunity to malaria. These factors include the absence of major histocompatibility antigens on the surface of infected RBCs; malaria antigen-specific immune unresponsiveness; and strain diversity of malarial parasites, along with the ability of the parasites to express variant immunodominant antigens on the erythrocyte surface that changes during the period of infection.

Methodology

This study was conducted among adult patients of falciparum malaria. All Adults patients (>14 yrs.) with positive asexual forms of malaria in thick smear, thin smear or positive QBC/ICT test admitted to the hospital were included in the study.

Severe malaria' was defined according to the World Health Organization criteria (WHO 1990 modified in 2000).5 In contrast to the WHO criteria; however, we used a practical definition of cerebral malaria: any impairment of consciousness or convulsions.

The diagnosis of plasmodium falciparum will be done by either Microscopy, QBC or lOT.

Criteria to diagnose AKI: Patients fulfilling the RISK criteria of RIFLE i.e. decreased urine output <0.5m1/kg/hr for 6 hrs, increased s creatinine x 1 .5 or INJURY criteria as increase in serum creatinine x2 or UO <0.5m1/kg/hr for l2hrs. AKIN criteria of acute kidney injury as increase in serum creatinine of 0.3mg/dI or >50% developing over <48hrs., or a urine output of <0.5m1/kg/hr for >6 hrs.

Exclusion criteria

> Known cases of chronic kidney disease.

All the patients will be investigated with

1) CBC (Complete blood count),
2) Serum electrolyte — Na, K.
3) Liver function tests (LFT)
4) Renal function test (RFT)
5) Serum urea & creatinine
6) Random Blood Glucose Test (RBS)
7) Serum cystatin C: 1 ml of serum sample is collected and quantitative assay is done by nephelometry. The serum sample is stable in 2-8°C for seven days.

Results

Table1: Age & Sex Distribution

Age Group in years	Male	Female	Total	%age
15-20	8	1	9	15%
20-30	9	6	15	25%
31-40	10	3	13	21.6%
41-50	8	3	11	18.3%
51-60	6	3	9	15%
61-70	1	2	3	5%
Total	42 (70%)	18 (30%)	60	100%

Our study subject included 60 cases of Falciparum malaria. Male patients contributed 70% (42 of 60) and females to 30%. Majority of the patients were in their 2' and 3rd decade of life, with mean age of 37±14.58 years.

Table 2: Clinical Parameters

Symptoms and Signs	No of patients	Percentage
Fever	58	96.6%
Vomiting	36	60%
Haedache	40	66.6%
Diarrhoea	12	20%
Altered Sensorium	17	28.3%
Convulsions	8	13.3%
Dicrease Urination	24	40%
Pallor	18	30%
Jaundice	23	38.3%
Hypotension	6	10%
Generalized Weakness	23	38.33%
Pulmnary aedema	03	5%
Hepatomegally	10	16.6%
Spleenomegaly	16	26.6

Fever was the most common symptom, present in 96.6% of the patients. Other symptoms were vomiting (60%), headache (66.6%), weakness (fatigue) 38.3%, Hepatomegaly and spleenomegaly was present 16.6% and 26.6% respectively.

Table 3: Heamatological & Biochemical Parameters

Hb (g%)	No of patients	Percentage
<5	1	1.66%
5-9.9	25	41.6%
10-12	31	51.6%
12-14	3	5%
Leucocytosis	8	13.3%
MP QBC)		
+	27	45%
++	22	36.66%
+++	11	18.33%
Hypoglycemia	4	6.66%
Hyperbilurubinemia	23	38.33%
Raised S. Creatinine	31	51.6%
Hyponatrermia	5	8.33%
Hypokalemia	2	3.33%
Urine		
Micro albuminuria	13	21 .66%
Microscopic hematuria	6	10%
Pus cells	7	11.66

Severe anemia fulfilling the criteria of severe malaria was present in one patient., 41.6% patients had their hemoglobin within 5 to 9.9g%. female patients contributed majority(64%). Leucocytosis was observed in 8 (13.3%). Raised serum creatinine and bilirubin was in 51.6% and 38.3% respectively. Few patients had hypoglycemia, hyponatremia and hypokalemia. Urine examination findings included microalbuminemia (21.6%), microscopic hematuria(10%) and urine pus cells in 11.6% of the patients.

Discussion

Malaria is the most important parasitic disease of humans caused by Protozoa of the genus plasmodium. The malarial parasite is transmitted by the mosquito vector of the Anopheles family. Although primarily a disease of the tropics, it is transmitted in 107 countries causing 1 to 3 million deaths each year. India harbours both P. vivax (50-55%) and P Falciparum (45-50%) and contributes 70% of malarial cases in south east Asia region. The prevalence of these two species is approximately equal in Indian subcontinent There is an estimated 70 to 100 million cases each year, but only 1.6 to 1.8 million cases are reported by the National vector Borne Disease control Programme (NVBDCP) [7].

Odisha state alone contributes 25% of the malaria incidence in India. According to NVBDCP report Odisha contributed 200958 cases of malaria in the year 2011. Out of which 183400 were falciparum malaria. In 2012, till August the number of cases of malaria were 575349 cases out of which 296121 were due to P. falciparum.

Approximately 2000 cases of malaria were admitted during the year 2011, falciparum malaria contributed to the majority of the cases 1470 of 2000 (78%) resulting mortality in 15% of the cases 97% of all the deaths were due to complicated malaria resulting from multiorgan dysfunction [8].

Malaria begins with non specific symptoms like headache, fatigue, abdominal discomfort and muscle aches followed by fever, Nausea, vomiting are common The fever often rises above 40°C with tachycardia and delirium. Generalised seizures are specifically associated with falciparum malaria. Slight enlargement of the liver and a palpable spleen are common [9].

Our study subject included 60 cases of Falciparum malaria. Male patients contributed 70% (42 of 60) and females to 30%. Majority of the patients were in their 2nd and 3rd decade of life, with mean age of 37±14.58 years.

In our study fever was the most common symptom, present in 96.6% of the patients. Other symptoms were vomiting (60%), headache (66.6%), weakness (fatigue) 38.3%, Hepatomegaly and spleenomegaly was present 16.6% and 26.6% respectively. Appropriately and promptly treated, uncomplicated malaria causes very low mortality (0.1%). However, once vital organ dysfunction occurs, the mortality can rise steeply. Manifestations - of severe malaria include unarousable coma/cerebral malaria, acidosis, severe normocytic normochromic anemia, renal failure, pulmonary edema (ARDS), Hypoglycemia, Hypotension/shock, Bleeding (Disseminated intravascular coagulation), convulsions and hemoglobinuria. Others include impaired consciousness (arousable), extreme weakness, hyperparasitemia and jaundice. The incidence of Jaundice, renal failure, pulmonary edema all relatively frequent in adult population

In our study the complications of severe malaria included were jaundice (38.3%), altered sensorium (13.3%), Hypotension (10.1%), decreased urination (renal involvement) 40%, Anemia (30%), Hypoglycemia (6.66%) and ARDS (5%). These complications occured either as single organ dysfunction or as in different combinations as multiple organ dysfunction (MOD). The incidence of complications were almost equal in both sexes (Male 52%, Female 48%).

The incidence of multi organ dysfunction was high (29 of 60, 48.33%). The most common two organ dysfunction was hepatopathy and AKI contributing to 23.33%, followed by cerebral malaria and AKI, 15%.

A prospective study done by Prof. Mohapatra MK [10] on the natural history and assessment of severity of organ dysfunction in complicated malaria, showed that CNS, hepatic and renal involvement (601 of 853, 70.4%) were the most common combination.

Commonly encountered three organ dysfunction in our study was hepatopathy, cerebral malaria and AKI, 6 out of 29 MOD

(20.6%), cerebral malaria, ARDS and AKI, cerebral malaria, Hypotension and AKI all contributing to 10% each to the multiple organ dysfunction.

Observed biochemical and hematological parameters were, severe anemia (Hb<5gm/dl) was seen in 1.66%, Hemoglobin in the range of 5-1 Ogm/dI was in 41.6% of the patients, majority of the patient with anemia were female (64%).

Leucocytosis was observed in 13.3% of the patients and all those patients were admitted with complications of severe malaria.

The quantity of parasites in the MP (QBC) showed 3 + in 18.33%, 2+ in 36.66% and 1+ in 45% of the cases. Majority of the 3+ patients had multiorgan dysfunction.

Conclusion

Study included 60 number of patients with falciparum malaria. 42 patients (70%) were male and 18 (30%) were female. Majority of the patients ware in their second and third decade of life. Serum cystatin C, a sensitive renal injury marker is estimated in all the patients. We excluded the known case of CKD patients from the study.

Fever, headache, vomiting, decreased urination, weakness, altered sensorium and joundice were the most common clinical features.

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