Chapter

109

Malaria in India

DHANPAT KUMAR KOCHAR, PARMENDRA SIROHI, SANJAY KUMAR KOCHAR

MALARIA SITUATION IN INDIA

Malaria has been a problem in India for centuries. Details of this disease can be found even in the ancient Indian medical literature like the 'Charaka Sanhita'. In the 30's the disease was rampant in the country and for the first time, to combat the menace of malaria, the government of India launched the National Malaria Control Program in April 1953. The program proved highly successful and within five years the incidence of malaria dropped to 2 million per year. Encouraged by this, the central government started the National Malaria Eradication Program (NMEP) in 1958 and by 1961 the incidence dropped to 50,000 cases per year. Since then the program suffered repeated setbacks due to technical, operational and administrative reasons and the cases started rising again[1,2].

In 1976, NMEP recorded highest cases (6.45 million) since resurgence. The implementation of urban malaria scheme (UMS) in 1971-72 and the modified plan of operation (MPO) in 1977 improved the malaria situation for 5-6 years. Malaria cases again reduced to about 2 million, but the impact was mainly on *vivax* malaria. Easy availability of drugs under the MPO prevented deaths due to malaria and reduced the morbidity. The *Plasmodium falciparum* containment program (PfCP) launched in 1977 reduced the *falciparum* malaria in the areas where the containment program was operated but its general spread could not be contained. *P. falciparum* showed a steady upward trend during the 1970s and thereafter. The rising trend of malaria was further facilitated by developments in different sectors.

Malaria at one time a rural disease, diversified under the pressure of developments into various ecotypes identified as forest malaria, urban malaria, rural malaria, industrial malaria, border malaria and migration malaria; the latter cutting across boundaries of various epidemiological types. Further, malaria in the 1990s returned with new features like vector resistance to insecticides; pronounced exophilic vector behavior; extensive vector breeding ground, created principally by the water resource development projects, urbanization and industrialization; change in parasite percentage in favor of *P. falciparum*; resistance in *P. falciparum* to chloroquine and other anti-malarial drugs; and resistance to chemical control of vectors. Malaria control now became a complex enterprise, and its management required decentralization and approaches based on local transmission involving multisectoral action and community participation. Realizing the difficulties in controlling/eradicating malaria, the NMEP was renamed as National Anti-Malaria Program (NAMP). During this period of resurgence of malaria, certain states of the Union of India like Uttar Pradesh, Bihar, Karnataka, Orissa, Rajasthan, Madhya Pradesh and Pondicherry were found to be worst affected, particularly with increasing incidence of *P. falciparum* infection. Most parts of India now experienced a high transmission of *P. vivax* malaria and Chloroquine resistant *P. falciparum* in the North- Eastern states, Orissa and some other parts of India. The high altitude states of Jammu and Kashmir, Himachal Pradesh and Sikkim are free from malaria because the transmission is low or very low in areas at an altitude >1800 meters[2,3].

There are four species of human malaria parasites, i.e. *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae* and *Plasmodium ovale*. In India, 60 to 65% of the infections are due to *P. vivax* and 35 to 40% are due to *P. falciparum*. Only few cases of *P. malariae* have been reported from Orissa and Karnataka. The life cycle of

the malaria parasite comprises of an endogenous asexual phase (schizogony) with multiplication in the human host and an exogenous sexual phase (sporogony) with multiplication in certain anopheles mosquito. The minimum time from infection by mosquito bite until the first appearance of the parasite in RBC is termed as the *pre-patent period*. The *incubation period* which is characteristic of each species is the time interval from entry of infection to appearance of clinical symptoms which occurs at the time when parasitemia reaches a sufficient density and is usually two days longer then the prepatent period. Incubation period ranges from 8 to 21 days depending on species, host immunity and climatic conditions. The asexual life cycle of parasite is essentially the same, except that the life cycle of *P. falciparum* and *P. malariae* do not have the persistent tissue phase (Hypnozoite stage). Schizogony is repeated until the increasing immunity or chemotherapy inhibits parasitemia. Schizogony periodicity is characteristic for each species and usually at least two cycles of schizogony in the blood must elapse before sexual forms appear in human malaria parasites other than in the *P. falciparum* in which gametocytes appear in peripheral circulation after the tenth day of patency. *Recrudescence* is renewed manifestation of infection due to the survival of erythrocytic forms as seen in *P. falciparum* and *P. malariae* infection. *Relapse* is renewed manifestation of infection arising from the survival of hypnozoites either at relatively short intervals or after long periods. In human malaria, the relapses are confined to *P. vivax* and *P. ovale* infection. Sexual cycle (Exogenous sexual phase) of the parasite is completed in female anopheles. The whole cycle is completed between 7 to 15 days depending upon the species.

The antigenic diversity is present among different malaria parasite species and also within the species. Among the *P. falciparum* blood stage antigens, there is a great diversity both between geographic areas and within the same area. Antigenic variations have also been demonstrated in the course of a single infection in *P. falciparum*. *Virulence* is expressed by the severity of acute disease in the non-immune persons and it differs greatly amongst the different species. Severe malaria is usually caused by *Plasmodium falciparum* infection but recently it had also been reported in *Plasmodium vivax* cases in Indian subcontinent. The relative immunity of infants to malaria has been attributed to maternal immunity,' low attack rate by vectors which could be due to low attractiveness and/ or lower exposure, the persistence of fetal hemoglobin and/or protective immunoglobin in mother milk. Each infection tends to raise the immune level and thus accelerates the clearance rate of parasitemia. Heavy inoculation may overwhelm the incipient immune response[4].

Genetic factors also affect the distribution of malaria in several ways. Sickle cell trait is associated with relative protection against *P. falciparum* especially cerebral malaria. The Duffy negative RBC is specifically resistant to penetration by *P. vivax* and this is the cause of non-presence of *P. vivax* in West Africa. The hemoglobin variants like Hb E seem to afford protection against cerebral malaria. Normal homozygous thalassemia patients have 2.1 times relative risk of morbidity than that of trait carriers. G6PD deficiency is associated with low prevalence and density of *P. falciparum*. Hereditary elliptocytosis provides resistance to penetration by all species as well as due to reduced membrane deformity. Anomalies for the receptors of *P. falciparum* in erythrocytes of several blood groups, which lack certain glycophorins in the cell membrane, are partially resistant to invasion by *P. falciparum*[4].

CLINICAL FEATURES

Uncomplicated Malaria

The clinical features of uncomplicated malaria are common to all the four species. Headache, muscular ache and pain, vague abdominal discomfort, lethargy, lassitude and dysphoria often precede fever by up to two days. The temperature rises erratically at first, with shivering, mild chills, worsening headache, malaise, and loss of appetite. If the infection is left untreated the fever in *P. vivax* and *P. ovale* regularizes to a two-day cycle (tertian) and in *P. malariae* to a three-day cycle. The fever in *P. falciparum* remains erratic for longer period and may never regularize to a classical tertian pattern. As the infection continues, the spleen and liver enlarge and anemia develops. Occasionally patients may have severe abdominal pain, constipation or diarrhea, and in some cases watery diarrhea is a prominent manifestation. *P. vivax* and *P. ovale* have a tendency to relapse after resolution of the primary infection[6].

Severe Malaria

Plasmodium falciparum malaria is a potentially lethal disease because of its ability to produce severe malaria, whereas death from acute *P. vivax*, *P. ovale* or *P. malariae* infections is very rare. There have been many case reports of severe *vivax* malaria in recent past but majority of them were not entirely convincing, except the recent documentation, which had reported 11 cases of severe *vivax* malaria from Bikaner (India)[7]. Almost all deaths in a patient of malaria is due to severe malaria and the

important manifestation of severe malaria (WHO - 2000) are cerebral malaria, multiple convulsion, hypoglycemia, acute renal failure, acidosis (Respiratory distress), jaundice, hemoglobinura (black water fever), severe anemia, shock, pulmonary edema (ARDS), abnormal bleeding and prostration (extreme weakness in children) (Table 1)[6]. About 1000 deaths are reported annually but these figures do not include cases treated in private and not for profit health facilities[5].

Cerebral Malaria

Cerebral malaria is a state of unarousable coma of more than 30 minutes duration having Glasgow coma scale less than 10/14 associated with or without convulsions in which bacterial meningitis and locally prevalent viral encephalitis has been excluded by relevant clinical and laboratory investigation and demonstration of asexual form of parasite in peripheral smear. Onset may be gradual or sudden following focal or generalized convulsion, confusion, drowsiness, delirium, and abnormal behavior with fever. Cerebral malaria is an acute widespread bilateral, symmetrical encephalopathy producing upper motor neuron signs. It may be associated with meningism, hypertonia, brisk deep tendon reflexes and extensor planter response, extensor posturing, decerebrate rigidity, decorticate rigidity and sustained upward deviation of eyes[6].

In an Indian study from Bikaner on 441 patients of strictly defined cerebral malaria who received treatment as per WHO guidelines using IV/oral quinine, apart from unconsciousness in all the case, the other observations were convulsion (21.31%), neck rigidity (19%), psychosis (5.21%), conjugate deviation of eyes (2.26%), extrapyramidal rigidity (2.25%), trismus (1.31%), decorticate rigidity (1.13%) and decerebrate rigidity (0.90%). One hundred forty five (32.87%) patients expired and mortality was higher among pregnant female (39.28%). The important neurological sequelae (Post malarial neurological syndrome) in survivors were psychosis in 15 (5.06%), cerebellar ataxia in 14 (4.72%), hemiplegia in five (1.68%), extrapyramidal rigidity (EPR) in four (1.35%), peripheral neuropathy in three (1.01%), EPR with trismus in one (0.33%) and isolated sixth nerve palsy in one (0.33%) patients and all showed complete recovery in further follow-up. The important observations of this study were stormy presentation, increased incidence of hemoglobinuria and jaundice, presence of neck rigidity, no prognostic relation to fundus abnormalities and high incidence of cerebellar ataxia and psychosis as neurological sequelae in survivors. Knowledge of self-limiting course of neurological sequelae may be helpful in reducing economic strain of expensive investigations and treatment. The convulsions may be focal/generalized or Jacksonian type. The CSF opening pressure is usually increased ≅ 160 mm Hg and CT head and MRI showed mild cerebral swelling, which is due to increased blood volume[8].

In a study of two hundred and fourteen adult patients (> 14 years) of strictly defined cerebral malaria, Kochar, et al observed retinal hemorrhage in 25 (11.68%), papilledema in 17 (7.94%), blurring of disc margins in 25 (11.68%), retinal oedema in six (2.8%), disc pallor in five (2.33%), vitreous hemorrhage and hard exudates in one (0.46%) each and subconjunctival hemorrhage in six (2.8%) patients. The important conclusion was that none of the above finding except disk pallor ($p < 0.05$) was associated with statistically significant mortality ($p > 0.05$); whereas any of the fundus findings in uncomplicated/complicated malaria was related to statistically significant mortality ($p < 0.05$). This observation was different from the previous observation in which presence of hemorrhage was related with increased risk of severity[9].

In another study from Bikaner, somatosensory evoked potentials were recorded in patients of cerebral malaria and the important observations were delayed absolute latency of N20, increased N13-N20 IPL, i.e. central conduction time distorted and along with dispersed waveforms of N9 and N20 peaks.[10] In a recently concluded study, CT scan revealed evidence of cerebral edema is 80 patients (67%). Two patients had evidence of lacunar infarction. Lumbar puncture and CSF manometry showed CSF pressure to be raised in 44 (34.92%) patients. It was not an agonal event, as many of these patients recovered with antimalarial drug and mannitol as adjuvant therapy. (Unpublished data, personal communication, Rourkella Group).

Hepatic Dysfunction/Jaundice

Jaundice is a common way of presentation in *falciparum* malaria in Indian adults. This is associated with conjugated or unconjugated hyperbilirubenemia and elevated enzyme levels. Mild jaundice may be due to hemolysis with S. bilirubin upto 5-6 mg% but very high levels can occur only due to associated hepatocyte dysfunction. As per WHO (2000), the signs of hepatic dysfunction are unusual[6] but in a clinical observational study from Northwest India, the authors had observed evidence of hepatic encephalopathy in 15 patients with asterexis in 9, impaired psychometric tests in 12 and altered mental state in 13 patients. Arterial blood

ammonia level was 120-427 mEq/l (310 +/- 98.39 mEq/l) and EEG findings included presence of large bilateral synchronous slow waves, pseudo burst suppression and triphasic waves. The range of serum bilirubin was 3-48.2 mg% (mean +/- SD 10.44 +/- 8.71 mg%). The ranges of AST and ALT levels were 40-1120 IU/l (294.47 +/- 250.67 IU/l) and 40-1245 IU/l (371.12 +/- 296.76 IU/l), respectively. Four patients died due to multiple organ dysfunction and the others made rapid recovery. There was a strong evidence of hepatocyte dysfunction and hepatic encephalopathy in some of these patients and a suggestion was made for revision of current guidelines of WHO[11].

In another Indian study from Bikaner, the histopathological examination of 20 patients revealed swollen hepatocytes (100%), malarial pigment deposition (75%), inflammatory infiltrates (60%), congestion of hepatocyte (50%), alongwith centrizonal necrosis in 25% of cases. The evidence of predominant conjugated hyperbilirubinemia, increased levels of AST and ALT alongwith evidence of hepatocellular necrosis in histopathological examination were taken as strong evidence of gross hepatocytic dysfunction and the term malarial hepatitis was justified.[12] The clinical evidence of jaundice and serum bilirubin, AST, ALT and alkaline phosphatase associated with malaria becomes normal after initiation of proper therapy in 1 to 2 weeks duration whereas the same phenomenon in viral hepatitis takes 6 to 8 weeks to come to baseline level. The difference in regression of jaundice in these two disease were statistically highly significant[13].

Similarly Devarbhavi et al from South India also observed that malaria can cause fulminant hepatic failure similar to viral infection in a repot on 25 patients. Impaired excretion of bile secondary to loss of microvilli in bile canaliculi and local disturbance of blood flow in sinusoids was suggested as the cause of cholestasis and hepatocyte dysfunction. Furthermore, Kupffer cell stimulation, alongwith endotoxemia and high levels of cytokines such as tumor necrosis factor, interleukin (IL) 6, and IL-10, may give rise to the hepatic, neurologic, and biochemical changes seen in malarial hepatitis simulating fulminant hepatic failure[14].

Ultrasonography in acute viral hepatitis commonly shows hepatomegaly with low echogenicity and thick gall-bladder wall. A study on 29 patients of malaria with jaundice the ultrasonography revealed hepatomegaly in 24, splenomegaly in 23, hepatosplenomegaly in 20 patients. Liver echogenicity was decreased in 7 patients, and gall-bladder wall thickness increased in 5 patients. These observations suggest that inflammatory changes similar to those seen in viral hepatitis also occurs in patients with malarial hepatitis[15].

Renal Dysfunction

Acute renal failure in malaria is usually oliguric (<400 ml/d) or anuric (<50 ml/d), but urine output may also be normal or increased. Acute renal failure is common and often lethal when urine output is <400 ml in 24 hours (children <12 ml/kg) with serum creatinine >3 mg% (>265 mmol/L) inspite of adequate rehydration. Daily urine output as well as serum creatinine estimation is most important parameter to assess renal dysfunction[6].

In a study from Varanasi the authors studied renal involvement in 81 cases of malaria (*P falciparum* 75, *P vivax* 2 and mixed infection 4). The evidence of clinical renal disease in the form of acute renal failure, electrolyte abnormality, abnormal urinary sediment and increased urinary protein excretion (>500 mg/24 hours) was found in 100%, 91.3%, 46.9% and 18.5% respectively. Volume depletion, hyperbilirubinemia, intravascular hemolysis and sepsis were responsible for ARF in 72.8%, 64.2%, 70.3% and 25.9% cases respectively. All the patients were managed with anti-malarial drugs and dialysis support was needed in 35 patients (43.2%). Prognosis of malarial acute renal failure was favorable with mortality rate of 18.5%. Multi-organ failure was the commonest cause of death (33.3%).[16] Mehta, et al from Mumbai studied 24 patients (PF–16, PV–3 and mixed infection–5). Non-oliguric ARF was seen in 14 patients, whereas 18 patients showed severe ARF (Serum creatinine >5 mg%) and 22 patients needed dialysis. Prolonged ARF lasting for 2-6 weeks was seen in eight. Seventeen patients recovered completely, while seven showed fatal combination of disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), severe ARF and PF malaria.[17] Prakash, et al from Varanasi reported ninety-four (15.5%) patients of ARF complicating malaria, amongst 607 cases of ARF of diverse etiology. There has been an alarming increase in the incidence of malarial ARF from 6.66% in 1995 to 27% in 1999. *Plasmodium falciparum* and *P. vivax* malaria were responsible for ARF in 76 (80.9%) and 11 (11.7%) patients respectively. Oligoanuria was seen in 65 (69%) patients and 72 (76.6%) cases required dialysis support. The etiologic factors contributing to the development of ARF included: volume depletion in 49 (51%), intravascular hemolysis in 37 (39.4%), heavy parasitemia in 34 (36%), hyperbilirubinemia in 31 (33%), hypotension in 29 (30.9%), sepsis in 9 (9.6%) and DIC in (7.4%) patients.[18] In a study on 2098 patients with ARF Naqvi et al from

Pakistan reported 124 (5.9%) patients due to malaria (*P. falciparum* 121 and *P. vivax* 3). Mean serum creatinine on admission was 9.43 ± 5.39 mg/dl and 99 (79.8%) patients required dialysis support. [32] (25.8%) patients died, most of them within 48 h of admission. Age, oliguria, central nervous system involvement and presence of DIC emerged as bad prognostic factors in simple univariate analysis. The number of dialysis sessions did not differ significantly between the oliguric and non-oliguric groups[19].

Pulmonary Edema/ARDS

The non-cardiogenic pulmonary edema in adult may occur even after several days of antimalarial therapy. It is often manifested when the patient is otherwise showing recovery from the disease. In some of these patients it is due to fluid overload whereas it may also be associated with normal or negative fluid balance along with normal or reduced pulmonary capillary wedge pressure. It is commonly associated with hypoglycemia, metabolic acidosis and renal failure. Hyperparasitemia and pregnancy are usual contributing risk factors. It resembles adult respiratory distress syndrome and may present as tachypnea and other chest signs. Pulmonary edema is more commonly seen in pregnancy especially during second stage of labor and is associated with high mortality[6].

Kochar, et al studied two epidemics in 1994 and 2003 and reported that incidence of pulmonary edema/ARDS had not changed in last 10 years and it varies between 2-3%.[20] In a study from Rohtak, Rajput, et al reported 4 patients of pulmonary edema out of one hundred malaria cases in which patients expired.[21] Similarly, Mishra, et al from Berhampur reported 2 patients out of 150 cases of malaria and both the patients expired.[22] Mehta, et al from New Delhi also reported two cases of pulmonary edema out of 425 cases of *falciparum* malaria.[23] Kochar, et al reported three cases of pulmonary edema/ARDS with *vivax* malaria out of 11 cases of severe *vivax* malaria[7].

Shock

The features of circulatory collapse are in the form of cold, clammy, cyanotic skin with constricted peripheral veins and systolic blood pressure of <80 mmHg. It is commonly associated with pulmonary edema, metabolic acidosis, massive hemorrhage, splenic rupture and gram-negative septicemia. Shock with gastrointestinal symptoms, dehydration, hypovolemia and hemorrhage is also called as algid malaria.[6] In an observational study from Bikaner the authors have observed that the incidence of shock has increased from 5.26 to 10.04% in a comparison study in 1993 and 2003.[7] The authors have also reported two cases of shock in *Plasmodium vivax* malaria infection.[20] Kumar, et al in a study from Vellore on children observed that apart from other complications shock and acidosis were present in 84% and 90%, respectively[24].

Hematological Abnormality

Severe anemia (PCV <15% or Hb <5 gm%) can develop rapidly in non-immune person and in unstable malarial transmission zone. It is usually normochromic normocytic and may be associated with confusion, restlessness, coma, acidosis and hemorrhage. Severe bleeding from gums, nose, or gastrointestinal tract occurs in <5% of patients. Hemetemesis may also occur from stress ulcer or from acute gastric erosions. Thrombocytopenia is an important feature seen in both *falciparum* and *vivax* malaria. Severe DIC may be important cause of severe bleeding from different parts of body[6].

In a study from Mumbai, Jadhav, et al observed that out of 1565 subjects studied the normal platelet count was present in 21.6% cases only. The mean platelet count in *vivax* malaria (n=973) was 1,15,390/microl (SD $\pm$64,580, range 8000-5,73,000/microl), as against *falciparum* malaria (n=590) where the same was 100,900/microl (SD $\pm$75,437, range 2000-497,000/microl) (Pearson coefficient 8.825, $p < 0.0001$). Platelet count < 20,000/microl was noted in only 1.5% cases in *vivax* malaria as against 8.5% cases of *falciparum* malaria, and none of the subjects with *vivax* malaria had a platelet count less than 5000/microl. Thrombocytopenia less than 20,000/microl can occur in *P. vivax* malaria although statistically more common with *P. falciparum* malaria. The above findings can have therapeutic implications in context of avoiding unnecessary platelet infusions with the relatively more benign course in *P. vivax* malaria[25].

Hemoglobinuria (Black Water Fever)

Dark red, brown or black colored urine is frequently observed in Indian patients. It is due to the massive intravascular hemolysis associated with hyperparasitemia. Only few patients develop renal failure because the hemoglobin is not nephrotoxic in a well hydrated person[6].

Hypoglycemia

It is more common in children, pregnant women and patients receiving quinine. At times it may be difficult to distinguish between cerebral malaria and hypoglycemia because both may present with coma and

convulsion when blood sugar level reaches <40 mg%. Prolonged hypoglycemia is associated with high mortality and permanent neurological damage[6].

In a prospective study of blood glucose level at the time of admission on 532 cases of severe malaria in Bikaner, Kochar, et al observed that eleven patients had blood glucose level < 40 mg% (< 2.2 mmol/L) and all were unconscious. Four patients became conscious with IV infusion of 25% dextrose only without receiving any specific antimalarial treatment. Recognition of these patients of "*falciparum* malaria with hypoglycemia" by blood glucose estimation at the time of admission can significantly alter the ultimate outcome. The mortality trend was more in patients having blood glucose level < 40 mg% (< 2.2 mmol/L) in comparison to group of patients having blood glucose level between 41 to 60 mg% (2.2 to 3.3 mmol/L) and was least in those having blood glucose level > 60 mg% (> 3.3 mmol/L)[26].

In an illustrative case reports Kochar, et al reported two patients who fulfilled the definition of cerebral malaria but were actually the patients of *falciparum malaria with hypoglycemia* and not the cases of cerebral malaria. A 60-year-old man was admitted with fever for 3 days, generalized convulsions for 8 hours, and unconscious (Glasgow coma scale 5) for 2 hours and blood film showed heavy P. *falciparum* parasitemia. Blood glucose level was 2.2 mmol/L and the patients became consicous by infusion of 200 ml of 25% within 20 min. He recovered completely on oral quinine within 7 days. In an another case, a 17 years old woman in the second trimester of her first pregnancy had a fever for 4 days. She became unconscious after having generalized convulsions and was admitted to hospital after 3 hours in coma (Glasgow coma scale 4). She was sweating profusely and had tachycardia. The blood glucose level was 2.0 mmol/L and a blood film showed asexual forms of P. *falciparum*. She was given 200 ml of 25% glucose and recovered from coma within 15 min. She was treated by oral quinine. These patients should not be included under the heading of cerebral malaria for research purposes[27].

Acid-Base Disturbance (Acidosis)

Severely ill patients with hypoglycemia, lactic acidosis, ARF, refractory circulatory failure and respiratory arrest may present with Kussmual's breathing having blood pH<7.25, serum bicarbonate level <15 mEq/L and serum lactate level >5 mmol/L. It is usually seen in children[6].

Hyperparasitemia and Systemic Infection

Hyperparasitemia is a term used when infected RBC is >2,50,000/µl or >5% in non-immune and >20% (>1000000 /µl) in any patient of malaria. Systemic infection especially salmonella bacteremia, chest infection and UTI may be commonly associated in severe *P. falciparum* malaria[6].

Cerebral Malaria in Pregnancy

Pregnant women constitute an important high-risk group for malaria infection which may cause abortion, still births, intrauterine growth retardation (IUGR), and pre-mature labor. It is more pronounced in primiparous women as compared to multiparous. *Falciparum* malaria in pregnancy carries a high mortality rate both for mother and child. Previously it was thought that during pregnancy there was immunosuppresion, which increases the susceptibility to malaria, but recent studies indicate that it is actually due to the parasites adhering to new receptors, available on the syncytiotrophoblasts during pregnancy, despite an otherwise normal functional immunity. This hypothesis can also explain the differences between severity of malaria in primigravida and multigravida, since the host becomes less and less susceptible to the placental adhesive variants with every subsequent pregnancy. The new receptors which may become available during pregnancy are chondroitin sulphate A and thrombomodulin. As the pregnancy is associated with increased incidence and adverse outcome of *falciparum* malaria, chemoprophylaxis should be made an integral part of antenatal care along with antianemic therapy to reduce the maternal and fetal complications.

In a study on two hundred eighty-eight admitted female patients of *falciparum* malaria out of which 45 patients were pregnant, Kochar et al reported that the mortality rate was highly significant in pregnant females (37.77%) in comparison to non-pregnant females (14.81%, p<0.001). The incidence of various complications were also more in pregnant females in comparison to non-pregnant females. The incidence of infection was higher among primigravida and second gravida 30/45 (66.66%) as compared to multigravida 15/45 (33.33%) and was common during 14-28 wk of gestation (23/45, 51.11%). Pregnancy related complications in the form of preterm live birth (20%), intrauterine death (IUD 31.11%), still births (13.33%) and abortions (11.11%) were more pronounced in primiparous women as compared to multiparous. Weight of placenta in majority of patients ranged between 200-400 g (22/31; 70.96%). Normal pregnancy continued in only 11 out of 45 pregnant females, out of which seven had low birth weight body (63.63%)[28].

Analysis of three years data from a malaria clinic operated by the Indian Council of Medical Research (ICMR) in Jabalpur, showed a statistically high

prevalence of malaria amongst pregnant women, in comparison to non-pregnant women. Cerebral malaria was the common complication and was more frequent in primigravida, falling progressively with increasing parity. Mean parasite densities were significantly higher in pregnant women compared with nonpregnant women for both *P. falciparum* ($P < 0.001$; df = 137) and *P. vivax* ($P < 0.05$; df = 72) infection. Pregnant women with malaria were significantly more anemic and the average weight of 155 neonates from infected mothers was 350 g less than that of 175 neonates from noninfected mothers. This difference in birth weight was statistically significant for both *P. falciparum* ($P < 0.0001$; df = 278) and *P. vivax* ($P < 0.0001$; df = 223) infection[29].

CHANGING TRENDS IN INDIA

The spectrum of severe *falciparum* malaria (Fig. 2) has changed worldwide. In India too, the scenario has changed dramatically. This was recently reviewed in a WHO sponsored workshop at Rourkela which revealed an increasing trend in favor of renal and hepatic failure and multiple organ dysfunction. Currently, a large proportion of cerebral malaria patients present with multiple complications including acute renal failure (ARF) and jaundice. The death rate is also very high in this group.

Kochar, et al (2006) studied two epidemics of malaria in Northwest Rajasthan during 1994 and 2001. There was a significant increase in the incidence of the jaundice 11.47 to 58.85% ($p<0.0001$), severe anemia 5.83 to 26.04% ($p <0.001$), renal failure 2.07 to 6.25% ($p<0.05$), spontaneous bleeding 9.59 to 22.4% ($p<0.001$), shock 5.26 to 10.94% ($p<0.05$) and thrombocytopenia 0.7 to 5.73% ($p<0.001$) along with significant decrease in cerebral malaria 25.75 to 10.94% ($p<0.001$) in the year 2001 in comparison to 1994. The incidence of other complications were almost same in both the years, but there had been a statistically significant ($p<0.001$) change from the occurrence of solitary complications — cerebral malaria in 1994 towards the multiple organ dysfunction in 2001 (9.59 to 22.4%), mostly because of concomitant presentation with hepatic and renal involvement in many patients and association of severe anemia. Death rate was also high in the patients having multiple organ dysfunction syndrome (MODS). Regarding solitary complications leading to death, shock and acute respiratory distress syndrome (ARDS) were the important terminal events in 2001 in comparison to cerebral malaria in 1994. The overall mortality in 2001 and 1994 was 10.93 and 11.09% respectively. The awareness about the changing spectrum of severe malaria is of great importance to every level health care provider. Today, in India with any level of transmission the possibility of *falciparum* malaria should always be suspected in a patient presenting with fever along with jaundice or renal failure[20].

Mohapatra, et al in 2006 from Orissa also observed that jaundice is an important solitary complications. The multiple complications were found in various combinations and majority (n=136, 42.5%) had constellation of 3 different complications. Cerebral malaria, jaundice, and renal failure (102 of 136, 75.3%) were the most common combination. As the population of patients progressed from single to multiple complications, increasing proportions had jaundice, renal failure, and anemia. 12.8 to 36.2% of patients in any category progressed from one complication to other complication within 72 hours. The mortality rate was 14.6%, 21.3%, 30.9%, 38.5%, 100% and 100% among patients with 1,2,3,4,5 and 6 complications respectively[30].

Severe *Vivax* Malaria

Plasmodium vivax infection is responsible for 60-70% of malaria cases in India and it is most important cause of morbidity. It is usually presumed to cause only uncomplicated malaria but in the last few years there had been many reports regarding *severe vivax malaria*. In a recent study from Bikaner the authors have reported 11 cases of definite severe *vivax* malaria. All these cases were diagnosed by clinical features supported by PBF positive for *P. vivax* and negative for *P. falciparum*, rapid diagnostic test (RDT) showing evidence of pLDH positive for *P. vivax* and HRP-2 and pLDH negative for *falciparum* along with PCR showing evidence of *P. vivax* only. All other infectious causes were ruled out by appropriate tests. In this study the manifestations observed were jaundice and hepatic dysfunction in four, renal dysfunction in four, severe anemia in four, cerebral malaria in three, ARDS in three, bleeding diathesis in one, hemoglobinuria in one and MODS in five patients. All patients were treated with IV / oral quinine. In this study two patients expired and both of them were having multiorgan dysfunction. Recently in a monograph on "treatment of malaria WHO 2006", the terminology of severe *vivax* malaria has been accepted separately and it had advocated the same regimen of treatment as we have used in our study[7]. Similarly, a good number of cases of severe *vivax* malaria have also been reported from different region of Indian Subcontinent but they lack in authenticity because of non-stringent diagnostic criteria. In all these reports the disease was diagnosed only by PBF examination, except in the study of Kochar, et al and Beg, et al[7,31].

Delayed Cerebellar Ataxia (DCA)

Post malarial neurological syndrome (PMNS) are known entities for decades. Delayed cerebellar ataxia is a new PMNS observed in Indian subcontinent during last two decades. In 1987, Senanayake from Sri Lanka reported few cases of delayed cerebellar ataxia as a complication of *falciparum* malaria. Later on in 1994 there was another report of 74 cases of DCA from the same region. In 1996 Kochar, et al reported 18 cases of DCA from Bikaner, Northwest India. The ataxic symptoms appeared after an afebrile period of 2-7 days and neurological examination revealed no other abnormality except a cerebellar syndrome interfering with normal gait and speech. Lower limbs were affected more than the upper limbs and the mean delay between onset of fever and onset of cerebellar ataxia was 13 days. All the patients improved within one month without any residual deficit. Further follow-up for next 4 weeks revealed no abnormality. Two cases of delayed cerebellar ataxia have been reported from Behrampur by Mohapatra[34].

In another study from Northwest India, Kochar et al reported patients with *P. falciparum* malaria presenting with signs of cerebellar dysfunction. In a study on 3188 admitted adult patients with *P. falciparum* malaria, cerebellar syndrome was observed in 49 patients at different stages of malarial infection. Cerebellar ataxia during the acute stage of the illness with normal level of consciousness was observed in 9 patients. There was selective involvement of cerebellum without any other neurological deficit except convulsions in three patients. Cerebellar ataxia as a neurological sequelae in survivors of cerebral malaria was found in 22 patients out of a total of 441 patients with strictly defined cerebral malaria whereas, delayed cerebellar ataxia was observed in 18 patients[32-34].

Drug Resistance

Kshirsagar, et al in 1995 from Mumbai reported that the single dose of (10 mg/kg) chloroquine which was highly effective in the past is not responsive with 20/56 patients of *P. falciparum*, 7/139 patients of *P. vivax* and 1/5 patients of mixed infection as evidence by smear positivity on day 6 or day 14. However, by increasing the dose to 25 mg/kg the response was obtained in 17/20 patients of *P. falciparum.* Three out of 20 cases of P. *falciparum* and 1/7 *P. vivax* cases did not respond to full dose (25 mg/kg) of chloroquine. These 3 chloroquine resistant cases of *P. falciparum* responded to sulfadoxine-pyrimethamine combination while the single case of chloroquine resistant *P. vivax* did not respond to quinine or sulfadoxine-pyrimethamine[35-37]. Later on, the same author observed that drug resistance is increasing in *Plasmodium falciparum*. They reported chlsoroquine

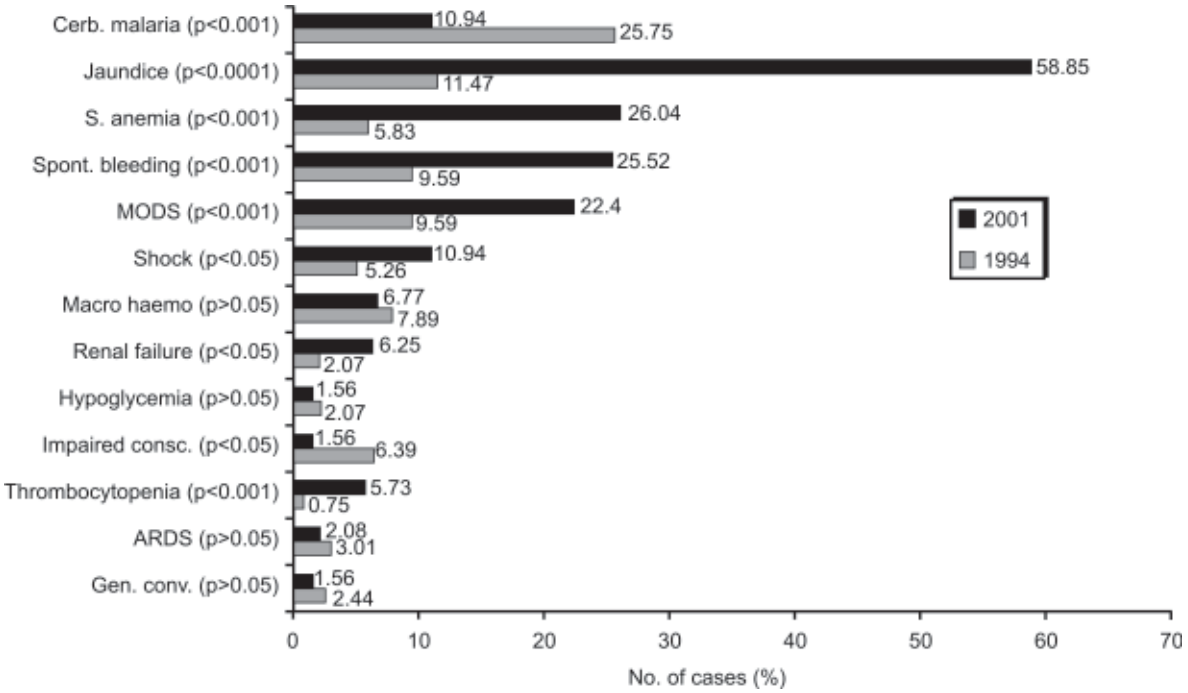

Fig. 1: The spectrum of severe malaria: 1994 vs 2001

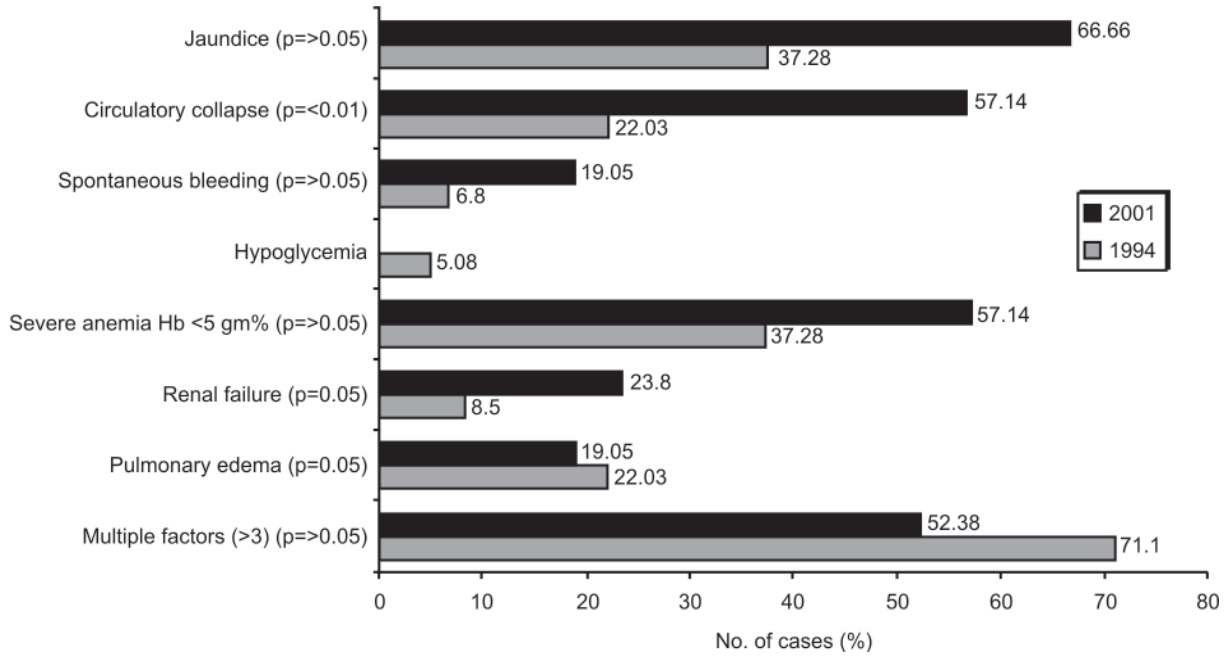

Fig. 2: Complications related to mortality in severe falciparum malaria patients: 1994 vs 2001

resistance figures of 36.78%, 45% and 53.8% in the years '94, '95 and '96 and the in vitro resistance figures of 41.17%, 54.28% and 66.6% in the same years[35-38].

A case of multi-drug resistant *P. falciparum* malaria was reported by Dua, et al from Kamrup district with chloroquine, sulfadoxine–pyrimethamine, and quinine sequentially. Similarly Singh, et al from Delhi in 1999 reported a fatal case of multi-drug resistant PF malaria from Delhi[39,40]. Rastogi, et al from Allahabad in 1991 reported that out of 92 cases of *Plasmodium falciparum*, 31 (33.7%) showed resistance to chloroquine and 61 (66.3%) were sensitive to the standard dose of chloroquine. Out of the 31 resistant cases, 19 (61.3%) showed resistance at RI level and 12 (38.7%) at RII level[41].

Mohapatra, et al in 2003 from Diburgarh, Assam reported that therapeutic failure was observed with chloroquine in 83.1% (44/53) and to both chloroquine and S-P combination drug in 44.1% (19/43) patients. Further, 15.8% patients (3/19) failed to respond even to quinine. Overall, 5.7 percent patients (3/53) showed unresponsiveness to all the three drugs, i.e. chloroquine, S-P combination and quinine. Asexual parasite clearance and fever clearance was slowest with chloroquine and fastest with quinine.[42] In a recent multicentric trial to study the therapeutic efficacy of chloroquine in *Plasmodium vivax* infection on 287 patients from different epidemiological region Neena Valecha et al recorded 100% cure rate at the end of 28 days and there was a rapid parasite clearance rate in all age groups form all study sites. This study confirmed the continued efficacy of chloroquine in *vivax* malaria in India[43].

The national drug policy for malaria in high-risk areas is advocating the full dose of chloroquine in chloroquine sensitive areas and a combination of artesunate and sulfadoxine–pyrimethamine in chloroquine resistant areas in uncomplicated malaria, Whereas all patients of severe malaria irrespective of chloroquine sensitivity of the region should be treated by IV quinine or artesunate. Since malaria is changing its facet from time to time; all the knowledge of this phenomenon is highly essential for every level health-care provider for administering effective management to the suffering humanity.

REFERENCES

1. Panda M, Mohapatra A. Malaria Control – An overview in India. J Hum Ecol 2004;15(2):101-4.
2. NAMP, DGHS Govt. of India: Malaria and its control in India-Country Scenario 1999.
3. Sharma VP. Re-emergence of malaria in India. Indian J Med Res 1996;103:26-45.
4. Shiv Lal, Sonal GS, Phukan PK. Status of Malaria in India. A report by National Anti Malaria Programme.
5. World Malaria Report by WHO 2005.
6. WHO Severe Falciparum Malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene 2000;94(1):1-73.

7. Kochar DK, Saxena V, Singh N, Kochar SK, Kumar SV, Das A. Plasmodium vivax malaria. Emerg Infect Dis 2005;11(1):132-4.
8. Kochar DK, Shubhakaran, Kumawat BL, Kochar SK, Halwai M, Makkar RK, et al. Cerebral malaria in Indian adults: a prospective study of 441 patients from Bikaner, north-west India. J Assoc Physicians India 2002;50:234-41.
9. Kochar DK, Shubhakaran, Kumawat BL, Vyas SP. Prognostic significance of eye changes in cerebral malaria. J Assoc Physicians India 2000; 48(5):473-7.
10. Kochar DK, Makkar RK. Somatosensory evoked potentials in cerebral malaria. A preliminary study. Electromyogr Clin Neurophysiol 1994; 34(5):301-7.
11. Kochar DK, Agarwal P, Kochar SK, Jain R, Rawat N, Pokharna RK, et al. Hepatocyte dysfunction and hepatic encephalopathy in plasmodium falciparum malaria. QJM 2003; 96(7):505-12.
12. Kochar DK, Singh P, Agarwal P, Kochar SK, Pokharna R, Sareen PK. Malarial hepatitis. J Assoc Physicians India 2003; 51:1069-72.
13. Kochar DK, Kaswana K, Kochar SK, Sirohi P, Pal M, Kochar A, et al. Comparative study of regression of jaundice in patients of malaria and acute viral hepatitis. J Vect Borne Dis 2006;43: 123-9.
14. Devarbhavi H, Alvares JF, Kumar SK. Severe Falciparum Malaria Simulating Fulminant Hepatic Failure. Mayo Clin Proc. 2005;80(3):355-8.
15. Kachawaha S, Pokharna R, Rawat N, Garg P, Badjatiya H, Kochar DK. Ultrasonography in malarial hepatitis. Indian J Gastroenterol 2003;22(3):110.
16. Maheshwari A, Singh AK, Sinha DK, Tripathi K, Prakash J. Spectrum of renal disease in malaria. J Indian Med Assoc 2004; 102(3):143, 146, 148 passim.
17. Mehta KS, Halankar AR, Makwana PD, Torane PP, Satija PS, Shah VB. Severe acute renal failure in malaria. J Postgrad Med 2001; 47(1):24-6.
18. Prakash J, Singh AK, Gujrati S, Maheshwari A. Acute renal failure in Malaria: Changing trends. Indian J Nephrol 2002; 12:113-7.
19. Naqvi R, Ahmad E, Akhtar F, Naqvi A, Rizvi A. Outcome in severe acute renal failure associated with malaria.Nephrol Dial Transplant 2003;18:1820-3.
20. Kochar DK, Kochar SK, Agrawal RP, Sabir M, Nayak KC, Agrawal TD, et al. The changing spectrum of severe *falciparum* malaria: a clinical study from Bikaner (northwest India). J Vector Borne Dis 2006;43(3):104-8.
21. Rajput R, Singh H, Singh S, Meena, Tiwari UC. J Indian Med Assoc 2000; 98(10):612-4.
22. Mishra US, Roy G. Pulmonary manifestation in malaria. Chest 2005;128.
23. Mehta SR, Naidu G, Chandar V, Singh IP, Johri S, Ahuja RC. Falciparum malaria—present day problems. An experience with 425 cases. J Assoc Physicians India 1989;37(4):264-7.
24. Kumar S. Management of shock in children with severe P. falciparum malaria Q J Med 2003;96:778.
25. Jadhav UM, Patkar VS, Kadam NN. Thrombocytopenia in malaria—correlation with type and severity of malaria. J Assoc Physicians India. 2004;52:615-8.
26. Kochar DK, Thanvi I, Kumawat BL, Shubhakaran, Agarwal N. Importance of blood glucose level at the time of admission in severe and complicated malaria. J Assoc Physicians India. 1998; 46(11):923-5.
27. Kochar DK, Kumawat BL. Cerebral malaria or Plasmodium falciparum malaria with hypoglycaemia. Lancet 1996; 347(9014):1549-50.
28. Kochar DK, Thanvi I, Joshi A, Subhakaran, Aseri S, Kumawat BL. *Falciparum* malaria and pregnancy. Indian J Malariol 1998; 35(3):123-30.
29. Singh N, Shukla MM, Sharma VP. Epidemiology of malaria in pregnancy in central India. Bull World Health Organ 1999; 77(7): 567-72.
30. Mohapatra MK. The natural history of complicated falciparum malaria – A prospective study. JAPI 2006;54:848-53.
31. Beg MA, Khan R, Baig SM, Gulzar Z, Hussain R, Smego RA Jr. Cerebral involvement in benign tertian malaria. Am J Trop Med Hyg 2002;67(3):230-2.
32. Senanayake N. Delayed cerebellar ataxia: a new complication of *falciparum* malaria? Br Med J (Clin Res Ed) 1987; 16;294(6582):1253-4.
33. Kochar DK, Kumawat BL, Kochar SK, Bajiya HN, Maurya RK. Delayed cerebellar ataxia—a complication of *Plasmodium falciparum* malaria. J Assoc Physicians India. 1996 Oct;44(10): 686-8.
34. Mohapatra MK, Panda BK, Das SP. Cerebellar ataxia in *falciparum* malaria—a report of two cases. Indian J Malariol. 2000;37(1-2):46-8.
35. Potkar CN, Kshirsagar NA, Kathuria R. Resurgence of malaria and drug resistance in *Plasmodium falciparum* and *Plasmodium* vivax species in Bombay. J Assoc Physicians India. 1995; 43(5):336-8.
36. Kshirsagar NA, Gogtay NJ, Rajgor D, Dalvi SS, Wakde M. An unusual case of multidrug-resistant *Plasmodium vivax* malaria in Mumbai (Bombay), India. Ann Trop Med Parasitol. 2000; 94(2):189-90.
37. Garg M, Gopinathan N, Bodhe P, Kshirsagar NA. Vivax malaria resistant to chloroquine: case reports from Bombay. Trans R Soc Trop Med Hyg 1995; 89(6):656-7.
38. Garg MR, Gogtay NJ, Kotwani RN, Bodhe PV, Kshirsagar NA. Resurgence of malaria in Mumbai—is escalating chloroquine resistance a cause? J Assoc Physicians India 1999; 47(4):377-9.
39. Dua VK, Dev V, Phookan S, Gupta NC, Sharma VP, Subbarao SK. Multi-drug resistant *Plasmodium falciparum* malaria in Assam, India: timing of recurrence and anti-malarial drug concentrations in whole blood. Am J Trop Med Hyg 2003; 69(5):555-7.
40. Singh S, Guleria R, Kumar S. Multidrug resistant fatal *falciparum* malaria in a pregnant woman in Delhi. J Assoc Physicians India. 1999 Mar;47(3):346.
41. Rastogi AK, Joshi PL, Bhattacharya M, Dwivedi S, Singh G, Raj B. Resistant falciparum malaria in an endemic area of Allahabad (U.P.). Indian J Malariol. 1991; 28(4):215-7.
42. Mohapatra PK, Namchoom NS, Prakash A, Bhattacharya DR, Goswami BK, Mahanta J. Therapeutic efficacy of anti-malarials in *Plasmodium falciparum* malaria in an Indo-Myanmar border area of Arunachal Pradesh. Indian J Med Res. 2003; 118:71-6.
43. Valecha N, Joshi H, Eapen A, Ravinderan J, Kumar A, Prajapati SK, Ringwald P. Therapeutic efficacy of chloroquine in *Plasmodium vivax* from areas with different epidemiological patterns in India and their Pvdhfr gene mutation pattern. Trans R Soc Trop Med Hyg. 2006; 100(9) : 831-7.