REVIEW
OF
LITERATURE
Cerebral Malaria and Neurological Complications:

Waiz et al (1990) analysed 55 cases of cerebral malaria and noted that the predominant clinical features were impaired consciousness with convulsion in febrile patients with temporary residence in the endemic zone. Younger people were more prone to develop this condition. Thirty two patients were between 18-25 years. Anaemia (63.63%) and jaundice (34.54%) were more common and splenomegaly (7.2%) was uncommon. Clinical features of cerebral edema/raised intracranial pressure were not evident in their study. CSF study was unremarkable except for raised pressure in 7 (12.65%) patients. Response to intravenous quinine was satisfactory and yet the mortality was 11%.

Looareesuwan (1992) et al studied the pathophysiology and management of cerebral malaria and stated that the pathophysiology of coma is believed to be brain anoxia from ischemia due to sequestration of erythrocytes containing mature parasites in cerebral capillaries and venules and postulated mechanism of sequestration Cytoadherence, rosette formation and decreased deformability of the erythrocytes. According to him, the management of cerebral malaria includes early diagnosis and early treatment of complications, correction of fluid and electrolyte imbalance and proper nursing care. He stated a high mortality (10-40%) in spite of these efforts.
Pasloske et al (1994) in their study stated that the special pathology of acute cerebral malaria appears to result from excessive adherence of infected cells in cerebral vessels coupled with occlusion of cerebral blood flow in microvessels by infected cell rosettes. According to them, several endothelial cell proteins have been identified as potential receptors for infected erythrocyte adherence to vascular endothelium, including thrombospondin CD36, intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and endothelial leukocyte adhesion molecule-1 (ELAM-1), and the receptor on infected erythrocytes that mediates adhesion to endothelial cells has been identified and a very large malarial protein on infected cells called PEFMP-1. This view is in accordance with that of Berendt (1989).

Wright et al (1993) in their study stated that the cerebrospinal fluid leukocyte count was the single most important in determining the correct diagnosis between cerebral malaria and meningitis (the CSF leukocyte count being unaltered in patients with cerebral malaria). They added that other data contributing to the differential diagnosis of cerebral malaria and meningitis included the number of days of fever before admission, the presence or absence of mutual rigidity and peripheral blood malaria smear.

They reported motality rates of 14.9% and 29.6% for cerebral malaria and meningitis respectively. They suggested that physicians cannot reliably discriminate between cerebral malaria
and meningitis without CSF analysis.

Hamann et al (1993) stated that falciparum variety of malaria is the most well known neurological complication, caused by P. falciparum and characterized by a fulminant course with disturbances of consciousness and facultative seizures or focal neurological deficits. Pathologically, disseminated vasculomyelinophagic disorders is seen. Immunological changes, vascular hypoxic disturbances and metabolic toxic factors contribute to these pathological findings. They described chorea, cerebellar ataxis, spinal disease, peripheral neuropathy, polyradiculitis and psychiatric disorders in the neurological complications of malaria infection.

Deb et al (1992) described 6 cases with mental confusion and abnormal behaviour, 10 with convulsions and unconsciousness and 1 with hemiplegia in a series of 35 patients of falciparum malaria with atypical presentation.

Chaudhary et al (1992) noted extrapyramidal syndrome in cerebral malaria. In their study, a 45 years old male was admitted with complaints of high grade intermittent fever with chills or rigors for 8 days. Spleen was 4 cms enlarged below left subcondal margin and was firm and nontendor. Patient was drowsy, having no signs of meningeal irritation but had generalized course tremors and cogwheel type of rigidity in all four limbs. Peripheral blood film was positive for P. falciparum and P. vivax. CSF pressure was raised but was otherwise normal. The patient was put on intravenous chloroquine and he become afebrile

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on the 4th day of initiation of therapy and on the 15th day the extrapyramidal features disappeared. According to them localized signs in cerebral malaria are due to diffuse involvement of brain parenchyma by P. falciparum leading to cerebral edema and these cases recover usually due to absence of brain infraction.

Mehta et al (1989) postulated that the possible mechanism of this cerebral involvement could be either hyperpyrexia possibly causing protein denaturation of cerebellar cortex or an immunological injury.

Mathur et al (1992) noted a case of falciparum malaria having subarachnoid haemorrhage - an unreported presentation. Subsequently, Saraswat et al (1994) reported another case of cerebral malaria presenting as subarachnoid haemorrhage. They had a 32 years male patient who presented with fever, headache, Vomiting, irritable behaviour and signs of meningeal irritation. Lumber puncture showed haemorrhagic CSF and peripheral blood smear was positive for P. falciparum. The patient responded to antimalarial and supportive treatment. According to them, the possible cause for this hemorrhage was ischemic infaracts of the meninges.

Anaemia and Recticulocytosis

Anaemia is a common complication of malaria, and extensive hemolysis may occur in association with very high parasitaemia. For the most part, hemolysis results from rupture of infected erythrocytes during schizogony, although the
magnitude of hemolysis tends to be greater than can be accounted for this process alone. Looareesuwan et al (1987). In their study on dynamic alteration in splenic function during acute falciparum malaria stated that splenic sequestration of erythrocytes in association with the development of splenomegaly probably contribute to the pathogenesis of anaemia. On the other hand, there is little compelling support for the notion that there is also an autoimmune basis for the anaemia.

Deh et al (1992) reported splenomegaly in 45.6% and hepatosplenomegaly in 25% of malaria cases.

Niazi et al (1995) reported that splenomegaly correlated with thrombocytopenia and was present in almost half of the cases of falciparum malaria.

Weatherall et al (1982) in their study on the anaemia of P. falciparum malaria stated that dyserythropoiesis can occur and peripheral reticulocytosis in response to the anaemia may be delayed even after treatment.

Phillips et al (1986) in their study on the importance of anaemia in cerebral and uncomplicated falciparum malaria stated that dyserythropoiesis, erythrophagocytosis and iron sequestration may contribute to the anaemia, in addition to hemolysis. They added that any hypothesis devised to explain hemolysis in malaria must taken into account sequestration of parasitized red blood cells and thus any calculation of red cell destruction which is based solely on the extent of peripheral blood parasitaemia
will under-estimate the instantaneous total parasite burden and its capacity for dynamic increase. They stated that nonparasitized red blood cells are also hemolysed. They reported that anaemia was more severe in those with secondary bacterial infections, renal impairment and in pregnancy, and the degree of anaemia correlated with the admission parasitaemia, total bilirubin, serum creatinine, the presence of retinal haemorrhages and schizontaemia, and regarded the degree of anaemia as an important indicator of disease, severity in cerebral malaria. They further added that in addition to haemolysis, a defective narrow response appeared to play a role in the pathogenesis of anaemia and in those who were severely anaemic, reticulocyte counts were often low although in uncomplicated infection parasite clearance was followed by a rise in reticulocyte count. They concluded that it seems likely that the parasitaemia or its association pathophysiology does suppress reticulocyte release in malaria. In their study, 94% of the 169 patients with cerebral malaria developed anamia.

Abdala et al (1990) also noticed dyserythropoiesis in human malaria.

Waiz et al (1990) in their analysis of 55 cases of cerebral malaria found anaemia in 63.63% patients.

Sharma et al (1992) reported anaemia to be present in 86.7% cases of falciparum malaria and all patients with severe anaemia (10%) (<6gm%) died.
Deb et al (1992) found mild anaemia to be present in 65.6% cases, moderate in 25.6% and severe in 8.5% cases of falciparum malaria with atypical presentation.

Gorski et al (1994) reported anaemia and thrombocytopenia in most of the malaria cases being studied by them.

Niazi et al (1995) reported to be present in 49.27% of malaria cases.

**Leukocyte Response**

Reiley et al (1971) studied the leukocyte response in 404 individuals with acute malaria. Leukopenia was observed in 33%, 37% and 31.2% and Leukocytosis in 5%, 2.5%, 5.3% of cases with falciparum disease, vivax disease and total patients respectively. They stated that the leukocyte response does not appear to be suppressed by chemotherapy even in those individuals who were leukopenic prior to institution of therapy since most showed an increase to normal levels while on specific therapy. The absolute eosinophil count was increased in 6.7% of total cases. The post treatment eosinophil count was increased in 30%. An increase in the absolute monocyte count was noted in 19% in the group. They concluded that leukocyte changes especially leukopenia and left shift in the differential count, occur in about a third of patients with acute malaria. Monocytosis is less frequent and eosinophilia occurs only following chemotherapy. These changes although nonspecific for malaria may be strongly suggestive and useful in evaluating patients with 'fever' of unkown
origin. When parasitemia is light and definitive diagnosis difficult to establish initially, the leukocyte pattern plus a compatible clinical picture should prompt on more vigorous diagnosis evaluation until malaria parasites are demonstrated or until the disease is reasonable excluded.

Sharma et al (1992) observed leukopenia in 6.7% and leukocytosis in 13.3% of cases with falciparum malaria. Deb et al (1992) also reported leukopenia in 65.6% and leukocytosis in 13.3% of cases with falciparum malaria.

**Platelet Response**

Thrombocytopenia is an well recognised complication of malaria. Dennis et al (1966 : 1967); Dennis and Conrad et al (1963) and Conrad et al (1969) reported thrombocytopenia in malaria and suggested that the platelets were being removed from the circulation by consumption in intravascular coagulation, and presented convincing evidence by showing depletion of coagulation factors and the presence of fibrinogen degradation products as well as thrombocytopenia.

Beale et al (1972) reported that of 33 cases of naturally occurring malaria being studied, 32 were found to have significant thrombocytopenia, but only one patient showed signs of bleeding. The lowest platelet level was 11,000/cmm and the platelet levels rose slowly over a period of 28 days. The fall in platelets occurred in both vivax and falciparum malaria alike. There was no evidence of intravascular coagulation in any case.

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and a rise in IgM was found in all 13 cases in which it was estimated. They stated that the mechanism of thrombocytopenia in malaria is still not fully understood. Finally they concluded that thrombocytopenia is the rule in acute attack of malaria and it is not associated with depletion of other coagulation factors in the mild case, and suggested that the platelets are removed at an excessive rate from the circulating blood, probably by the reticuloendothelial system, and that they are in some way altered immunologically, which assists in their removal.

Mohanty et al (1988) described changes in circulating platelets of 26 patients with acute malaria and observed thrombocytopenia in 10 out of 15 patients with falciparum malaria and 4 out of 9 patients with vivax malaria. They reported platelet antibody to be present in 8 out of 11 patients being investigated and stated that inverse relationship between the platelet count and platelet antibody levels in serum supported the view that thrombocytopenia in malaria may be partly immune mediated.


Gorski et al (1994) observed profound anaemia and thrombocytopenia in the majority of patients with malaria and suggested that the destruction pathways of the erythrocytes and blood platelets may be similar as are the reasons for ineffective
erythro or thrombocytopoiesis.

**Hemostatic profile**

Sharma et al (1992) studied the coagulation profile in acute falciparum malaria and found FDP levels to be raised in 16.7% (5/30) cases. In their study, 2 cases had prolonged bleeding time with overt bleeding manifestation in one; and coagulation profile was normal in uncomplicated cases as compared to deranged one in complicated cases.

**Renal Involvement in Malaria**

Renal involvement is a complication of severe malaria and manifestations may occur as oliguria, anuria and any presentation of acute renal failure. Renal involvement is assessed by various renal function tests.

TT, Trang NH phu, H vint, DJ waller et al (1992)

Sixty four patients with malaria associated renal failure (of whom 12 died) were compared to 66 patients with severe malaria whose serum creatinine level remained >250mmol/L (six died) MARF was significantly associated with liver dysfunction. A fatal outcome was associated significantly with anuria, a short history of illness, multisystem involvement and high parasitemia. Most patients died from complications related to renal failure. The median (range) time until urine output exceed 20ml/(kg/d) was 4 days and the time for serum creatinine level to return to normal was 17+/-6 days. MARF can be managed...
effectively by prompt and careful peritoneal dialysis.

Rajapurkar et al (1994) described renal involvement in malaria from January 1988 to 1992, in his hospital 797 (5.69%) episodes of malaria were diagnosed on peripheral smear in 14006 patients. Out of these 730 (91.5%) were P. vivax and 67 (8.7%) were P. falciparum 12 out of these 730 vivax cases which had abnormal renal function, 11 out of 67 P. falciparum had acute renal failure.

Sowunmi et al (1996) assessed renal function in 40 children during acute illness and after recovery from falciparum malaria. Creatinine clearance was significantly lower during acute illness than after recovery. Six of the 18 children with impaired creatinine clearance had evidence of acute tubular dysfunction. Hyponatremia occurs in 12.5% during acute phase. Fractional sodium excretion (\(l'e\) Na) was raised in 27% during acute illness and continuing sodium wastage occurred in 17% after recovery. Plasma potassium was significantly higher and fractional potassium excretion (\(l'e\) k) was. Significantly lower during acute illness than after recovery there was a positive correlation between \(l'e\)Na and \(l'e\)k both during and after recovery from illness but they did not exactly mirror each other in every individual, urine sodium : Potassium ratios were similar during and after recovery from illness and was treated to \(l'e\)Na. Fractional glucose excretion was zero. Mild proteinuria occurred in 40% during acute illness but were not related to creatinine clearance, body temperature and presentation or peripheral para-
site density. Proteinuria was absent after recovery.

AK Sharma, Mamta Arora, H Gupta, R Gupta et al (1998) Thirty six of acute renal failure due to plasmodium falciparum malaria were studied. Mean age was 33.4±12 years and male : female ratio 4:5:1. Associated risk factor were jaundice (22.2%), severe acidosis (11.1%), cerebral complication (11.1%), gastrointestinal bleeding (8.3%), shock (8.3%), severe hypoglycaemia (5.5%) and pregnancy (2.7%). There was no evidence of intravascular haemolysis indicated by absence of haemoglobinuria. Kidney biopsy (n=6) showed acute tubular necrosis.

Liver Functions

Mishra et al (1992) performed liver function tests in 165 hospitalized patients suffering from P. falciparum malaria and reported that serum bilirubin was found increased in 33 (20%) patients. Serum alanine aminotransferase was increased in 5 (3.03%) patients, but only to mild to moderate levels. They concluded that though hepatomegaly and mild elevation of enzymes can be observe in a significant proportion of patients, involvement of liver leading to acute hepatitied or liver cell necrosis is a relatively uncommon complication in P. falciparum malaria.

Deb et al (1992) observed icterus in 5.7% (2 out of 35) patients with falciparum malaria.

Sharma et al (1992) observed hyperbilirubinemia in 23% of cases with normal AST and ALT and attributed this hemolysis of erythrocytes.
Ahsan et al (1993) reported six cases of falciparum malaria who presented with persistent fever, jaundice, encephalopathy and hepatomegaly with only modest elevation of liver enzymes and alkaline phosphatase. They added that liver biopsy is valuable in establishing the diagnosis of all stages of the disease.

**Blood Glucose and Malaria**

Sherman et al (1979) reported that in animal malaria parasitized red blood cells consume up to 75 times more glucose than uninfected cells, with lactate as the end-product of glycolysis. This factor may contribute to hypoglycemia in the severe case with high degree of parasitaemia.


Hypoglycemia is strongly associated with pregnancy. Gillmer et al (1975) stated that the functional hyperactivity of the pancreatic beta cell in pregnancy, associated with peripheral insulin resistance, may amplify the response to beta cell stimulation by quinine. In addition, Metzger et al (1982) stated that the biochemical response to fasting and development of hypoglycemia are accelerated in late pregnancy (accelerated starvation).

White et al (1983) studied the occurrence, clinical manifestations and mechanism of hypoglycemia in patients with
falciparum malaria. In their study, a total of 17 patients had hypoglycemia: 3 were pregnant or had recently delivered and had otherwise uncomplicated disease, and 14 had severe falciparum malaria (12 with cerebral malaria and 2 with hyperparasitemia and acute renal failure) and the overall incidence of hypoglycemia in cerebral malaria was 8 percent (12 of 151 patients), but 5 of the 10 (50%) pregnant women had hypoglycemia. Hypoglycemia in their series of patients was associated with marked hyperinsulinemia. The role of hyperinsulinemia in the development of hypoglycemia was further supported the evidence of glycogen in the livers of some fatal cases and by the rise in blood glucose after intravenous glucagon both of which suggest that glycogen stores were not always exhausted. They believed that reduced glucose supply (impaired hepatic glycogenolysis and gluconeogenesis) and increased demand (hyperinsulinemia, parasite use and anaerobic glycolysis in hypoxic tissue) contribute to this complication.

Deb et al (1992) reported random blood glucose value of less than 100 mg dl in 29 of the 35 falciparum malaria patients.