Gastrointestinal and Liver Involvement in Falciparum Malaria

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ABSTRACT

Nausea and vomiting are common symptoms found in falciparum malaria, particularly in children with high fever. Vomiting may be provoked by antimalarial drug treatment. While diarrhea has been reported from some parts of the world, it appears to be uncommon in others. Although malabsorption of amino acids, sugars, fats, chloroquine and quinine have been documented, in most studies the absorption of oral antimalarials in uncomplicated malaria has been normal in even the most seriously ill patients. In the acute phase of severe falciparum malaria, patients show the greatly reduced absorption of those sugars that rely on mediated mechanisms and unmediated diffusion. Absorption returns to normal in convalescence. Gastric emptying is normal in uncomplicated falciparum malaria. Biopsies of the gut show parasite sequestration in the vascular bed which presumably interferes with the process of absorption. Gastrointestinal permeability is increased during severe and uncomplicated falciparum malaria but reverts to normal in convalescence. Endotoxemia may also originate in the gut. Gram-negative bacteria or endotoxin may shift from the gut lumen; the normal hepatic clearance mechanisms may fail.

Hyperbilirubinemia is attributable to intravascular hemolysis of parasitized erythrocytes and to hepatic dysfunction and possibly to an element of microangiopathic hemolysis associated with disseminated intravascular coagulatiôn. Impairment of hepatic function is common in severe malaria. Unfortunately, assessment of ùliver functionû by measurement of blood concentrations of bilirubin and liver-related enzymes is notoriously imprecise, particularly in the presence of coexisting hemolysis, Jaundice is more common in adults with severe malaria than in children. The measurable consequences of hepatic dysfunction are coagulation abnormalities resulting from failure of clotting factor syntheses, hypoalbuminemia, and reduced metabolic clearance of many substances, including alanine, lactate, and antimalarial drugs. The biotransformation of drugs, particularly those metabolized by hepatic microsomal enzymes, is reduced in proportion to disease severity. Hepatic blood flow is reduced during acute malaria and is significantly lower in severe malaria than in uncomplicated malaria; it returns to normal during convalescence. Hepatic microsomal metabolism is also apparently slow in severe falciparum malaria but reverts to normal in convalescence. Liver metabolic function does not appear to be significantly affected in uncomplicated malaria.

Key words : gastrointestinal, liver, falciparum, malaria

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Dyspepsia including nausea, vomiting and epigastric pain is common in patients with acute falciparum malaria. Dyspepsia is correlated with endoscopic pangastritis, especially endoscopic antral gastritis[1] and the severity of the dyspepsia may increase as the antral histopathology becomes more evident. Minor stress ulceration of the stomach and duodenum is not unusual in severe malaria as it is in other serious infections. The pattern of malabsorption of sugars, fats, and amino acids suggests reduced splanchnic perfusion, even in uncomplicated malaria[2]. This results from both gut sequestration and visceral vasoconstriction. In addition, gut permeability may be increased and reduced local defenses against bacterial toxins or even whole bacteria in severe disease may be impaired. Increased small intestine permeability in patients with severe malaria persists for at least a week following treatment[3]. Antimalarial drug absorption from the gut is remarkably unaffected in uncomplicated malaria. Although gastric emptying time is not changed in uncomplicated malaria[4], gastric emptying time in severe malaria may be prolonged.

There are relatively few reports about the frequency of diarrhea in malaria. Diarrhea attributable to malaria is thought to be more common among children and nonimmune adults with hyperparasitemia. The reported incidence of diarrhea during malaria varies from 5 to 38%[5]. The pathology of patients infected with malaria is very complex and involves many organs, including the small bowel. However, the causes of gastrointestinal disorder associated with malaria remains unclear, and the mechanism of malaria-related diarrhea is likely to be multifactorial. Massive gastrointestinal bleeding with multiple mucosal hemorrhagic foci has been shown and is well demonstrated. Tumor necrosis factor has been implicated in malaria and free oxygen radicals which can cause tissue injury in the liver, pancreas and intestine are enhanced during malaria infection; and may give rise to a variety of disorders of the digestive system, including diarrhea and intestinal bleeding. Prostaglandins and cyclic AMP may also be involved in the development of diarrhea in malaria.

Histological studies of the gastric and intestinal mucosa (Figures 1 a and b) have shown parasitized erythrocytes sequestered in capillaries[6]. This sequestration may cause stasis and anoxia in the immediate vicinity of the enterocytes and tight junctions, leading to altered permeation of monosaccharides and disaccharides.

Hepatomegaly (Figure 2a) is significantly more common in the younger than in the older children. Complete resolution occurs in some 48% following antimalarial chemotherapy[7]. Routine clinical measurement of the size of the liver in children with hepatomegaly during acute uncomplicated Plasmodium falciparum malaria may be of some use when monitoring the therapeutic responses. The resolution of hepatomegaly, being a reflection of pathological changes, lags behind the clearance of parasitemia in children with P. falciparum malaria; the tendency for the hepatomegaly to resolve supports the use of the liver "rate" as a malariometric index for assessing the intensity of transmission in endemic areas.

Hepatic dysfunction is usual finding in severe malaria, particularly in adults[8-10]. Jaundice is com-
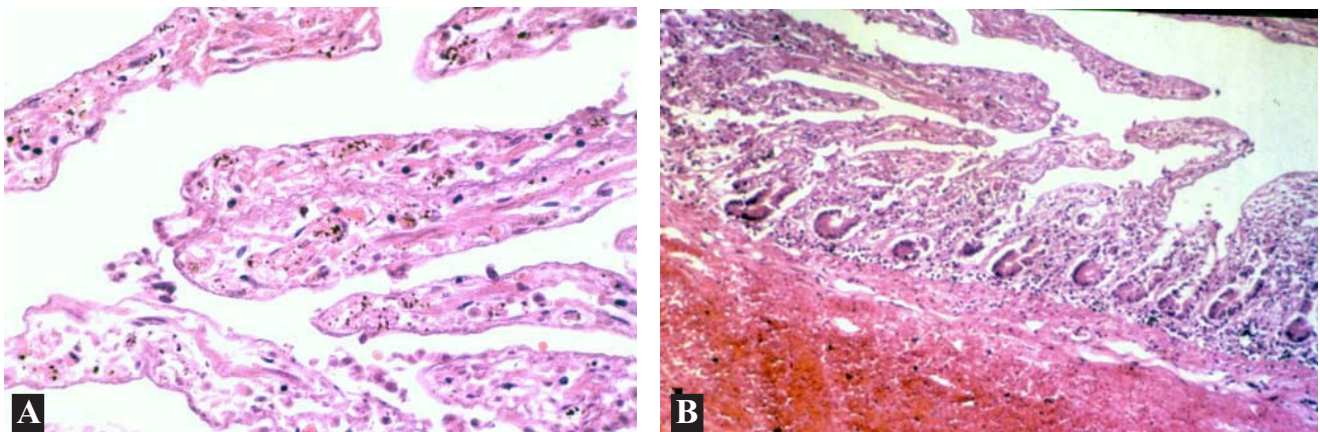
Figure 1. A) Parasitized erythrocyte sequestration in small intestine, predominantly within lamina propria capillaries of fatal falciparum malaria patients (H&E stain, × 200); B) Submucosal hemorrhage (H&E stain, × 100)
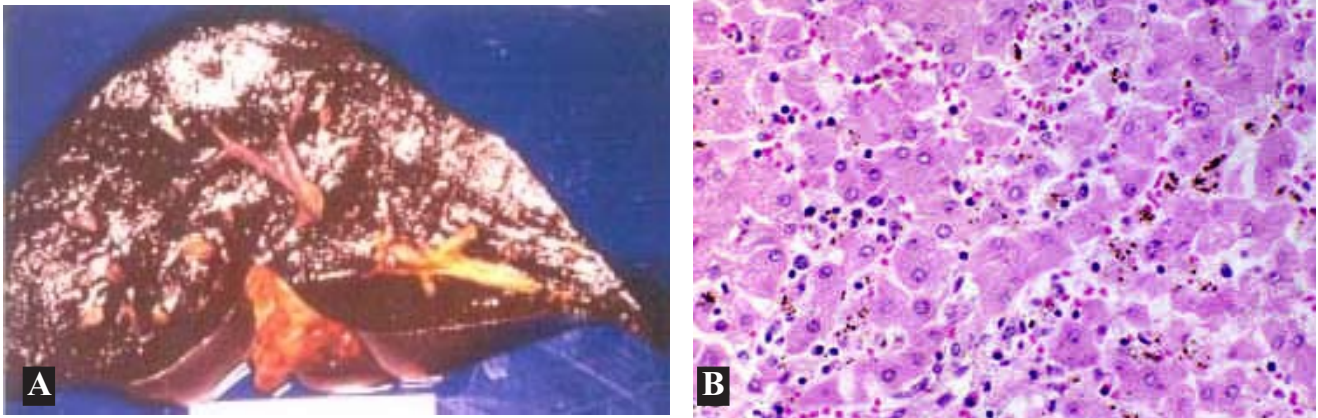
Figure 2. A) Enlarged liver in fatal falciparum malaria patient showing dark colored due to deposited malarial pigment; B) Hepatic sinusoids are dilated and congested with hypertrophied Küpffer's cells-laden malaria pigment, variable mononuclear cells, and parasitized erythrocytes (H & E stain, × 400)

mon. There are reductions in clotting factor synthesis, the metabolic clearance of drugs, and in biliary excretion; there may be a failure of gluconeogenesis, which contributes to lactic acidosis and hypoglycemia. The prognostic significance of jaundice depends on the context and is only noteworthy in the presence of other indications of severity. Deep jaundice in a child with malaria is probably not due to malaria per se and should prompt a search for an alternative explanation. True liver failure- a fulminant hepatitis is most unusual.

Most falciparum patients with jaundice have mild or moderate hyperbilirubinemia. Severe jaundice, usually accompanied by only moderate elevation of hepatic enzymes, may have resulted from hemolysis rather than from hepatic damage, a possibility that is consistent with our previous report[10] which showed that severe malaria is associated with elevation of indirect hyperbilirubinemia. Hepatocellular dysfunction in falciparum malaria is non-specific and may result from anoxia secondary to reduced or sluggish portal blood supply or sequestration or microcirculatory obstruction of the portal circulation. Indeed, jaundiced patients may be diagnosed as having "malaria hepatitis".

Elevations in AST and ALT levels were noted upon admission; AST level were often higher than ALT level[10,11]. Neither of these phenomena was a usual feature of patients with hepatitis A, B, or C. In severe falciparum malaria, hemolytic erythrocytes or ischemic hepatocytes may cause comparatively high level of AST, especially in the early stages of cerebral malaria. Similar values for AST, ALT, bilirubin, alkaline phos-

phates, and prothrombin time in survivors and non-survivors of cerebral malaria suggest that both groups were affected by similar hepatocellular damage: thus, mortality in patients with cerebral malaria does not therefore appear to be related to hepatic injury[11]. In contrast, less favorable coma scores, acute renal failure, and acidemia were more frequently associated with a fatal outcome[11-13]. Hepatic involvement in cerebral malaria is not associated with or predictive of outcome; mortality is attributable to other markers of malarial severity, such as renal failure and acidosis, rather than liver dysfunction. Comparing with falciparum malaria, the patients with P. vivax, P. malariae and P. ovale infections had slightly elevated serum bilirubin, aminotransferase and alkaline phosphates levels, and hypoalbuminemia; these minor abnormalities returned to normal within a few weeks after treatment[14].

There is some sequestration in the hepatic microvasculature, and in very severe falciparum malaria infections liver blood flow is reduced. Liver blood flow values, estimated by indocyanine green (ICG) clearance, of less than 15 ml/kg/min are associated with elevated venous lactate concentrations[2]: this suggests that blood flow limitation impairs lactate clearance, thereby producing a mechanism for the development of lactic acidosis. However, most patients with acute falciparum malaria have elevated liver blood flow values. Malaria and other infections impair the metabolic clearance of drugs: in uncomplicated malaria this is related to reduced metabolic activity and not to reduced liver blood flow. The activities of a broad range of the cytochrome P450 (CYP) mixed function oxi-

dases are reduced; including CYP3A4, which is responsible for quinine-3-hydroxylation, the principal route of quinine metabolic clearance, may be impeded. Clearance reduction is directly proportional to disease severity[15]. Hepatic microsomal enzyme activity is also reduced in severe malaria and reverts to normal in convalescence[16]. Jaundice in malaria has hemolytic, hepatic, and cholestatic components. Cholestatic jaundice may persist well into the recovery period.

Pathology of falciparum malaria patients usually reveals Küpffer's cell hyperplasia and mononuclear cell infiltration (Figure 2b); in addition, pigment deposits are prominent. Centrizonal necrosis has been reported. An immunohistochemical study of a patient with fatal cerebral malaria revealed that monoclonal antibodies to tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFNγ) had reacted with the hepatocytes around the central vein[17].

Parasite of the genus Plasmodium is the causative agent of malaria, an infection that is prevalent in tropical areas and which is marked by severe anemia. Whatever the cause, the continuing anemia appears to be related to the degree of hepatic dysfunction on admission[18]. The parasite is complex; its biphasic life cycle requires both an arthropod and a human host. The liver of the human host is the obligatory venue for the exponential amplification and molecular alteration of the parasite prior to the invasion of red blood cells. Natural exposure to the parasite results in incomplete and short-lived immunity, which fails to prevent intermittent episodes of parasitemia. Antibody responses to blood-stage antigens rather than a cellular response to pre-erythrocytic (liver) stage antigens are thought to mediate immunity induced by natural exposure to infection. Jaundice is one of clinical criteria of severe malaria[9].

In summary, gastrointestinal symptoms- particularly dyspepsia- are common in falciparum malaria. Jaundiced malaria patients have transient liver impairment which suggests that it is predominantly hemolysis rather than liver damage or cholestasis. Hepatic blood flow and hepatic microsomal enzyme activity are reduced in severe malaria but revert to normal in convalescence. Malaria complications are more frequent in jaundiced patients.

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