Jaundice in Falciparum Malaria

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Malaria remains an overwhelming problem in the tropical developing countries, with 300 to 500 million new cases, and about a million deaths per year. Malaria is a potentially life-threatening disease in the tropics. According to the World Health Organisation’s criteria, the recognition of one or more of the following clinical features should raise the suspicion of severe malaria: cerebral malaria (unrousable coma), severe anaemia (haemoglobin <5 g/dl), renal failure (serum creatinine >3 mg/dl), pulmonary oedema or adult respiratory distress syndrome (ARDS), hypoglycaemia (glucose <40 mg/dl), circulatory collapse or shock, disseminated intravascular coagulation (DIC), repeated generalised convulsions, acidosis (pH <7.25), macroscopic haemoglobinuria, hyperparasitaemia (>5 percent of the erythrocytes infested by parasites), or jaundice (bilirubin >3 mg/dl). A number of patients with malaria develop severe manifestations, and these patients require the most urgent and intensive care. Mortality among patients with cerebral malaria, even when treated in a modern intensive care unit, exceeds 30%; and when complicated by the adult respiratory distress syndrome, it may approach 80%. Mortality remains a serious issue because of failure to obtain and use preventive measures, delay in seeking medical attention, and misdiagnosis1,2,3.

Jaundice is one of the common severe manifestations of falciparum malaria. Its incidence varies between 10 to 45% in different reports, and is seen more in adults than in children. It may be present alone or with other complications. A study from Vietnam reported that 63% of the adults who had acute renal failure were jaundiced vs 20% of those without renal failure4. Similarly, half of the patients with cerebral malaria were associated with jaundice. Presence of jaundice in falciparum malaria indicates a more severe illness with higher incidence of complications. Mortality also was higher in the group of patients with jaundice (40% vs.17%; $\chi^2 = 4.85, p < 0.05$)5.

Jaundice may vary from mild to very severe. However, clinical signs of hepatic encephalopathy (such as liver flaps) are never seen unless there is presence of concomitant viral hepatitis6. Tender hepatomegaly and splenomegaly are common findings in all human malaria, and most commonly in young children. Recovery from jaundice is usually faster than the hepatitis, which usually takes a longer time to return to normal. A high bilirubin level should alert the clinician to look for black water fever and/or acute renal failure in some patients6.

Malarial hepatitis, jaundice, and hepatic dysfunction have been loosely interchanged. This has caused confusion and misconception. Liver is the first organ to be affected in a case of P. falciparum malaria. After the initial stage (pre-erythrocyte schizogony), merozoites are released into the blood stream. They do not have exo-erythrocytic schizogony. But in the patients of severe malaria, liver may be involved to different extents.

Liver biopsy/necropsy usually shows Kupffer cell hyperplasia, mononuclear cell infiltration, and pigment deposits; while other studies have demonstrated either no structural change or slight hepatocyte swelling. Centrizonal necrosis has also been reported. But unfortunately, studies are scant from our country7,8. In this issue of JIACM, an article pertaining to the histopathological study in severe malaria (p. 34) should interest you.

Impairment of hepatic function is common in severe malaria. It leads to improper handling of drugs and antimalarials (as evidenced by hepatic blood flow measurement – indocyanine green (ICG) clearance). In severe malaria, ICG clearance is significantly lower than in patients with uncomplicated malaria. It returns to normal during convalescence. Acute malaria also adversely affects the function of cytochrome P450 microsomal enzymes9. Unfortunately, assessment of liver function by measurement of blood concentrations of bilirubin and liver enzymes is imprecise, particularly in presence of

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haemolysis. So, it becomes difficult to state whether the index patient is having hepatic dysfunction or not. As we have seen, there may be some element of hepatic dysfunction, but to state that hepatitis is present in this situation is erroneous.

Jaundice in severe P. falciparum malaria is multifactorial
- Intravascular haemolysis of pRBCs.
- Haemolysis of non-pRBCs (innocent bystanders).
- Possibly micro-angiopathic haemolysis associated with DIC.
- Hepatic dysfunction.
- Associated haemoglobinopathies (not uncommon in malaria-prone areas).
- Drug-induced haemolysis (including quinine, etc.).
- G6PD deficiency, etc.

The laboratory findings
Hyperbilirubinaemia is mostly of unconjugated type. Often jaundice is mild, and total serum bilirubin is below 5 mg/dl, but at times bilirubin rises beyond 50 mg/dl. Enzymes are usually raised (within 3 to 8 times), alanine transaminase (ALT) never reaches to the level of viral hepatitis. 5’ nucleotidases and GGT concentrations may be moderately elevated. Hypoalbuminaemia is also seen in these patients. Prothrombin time may be moderately prolonged. Other abnormalities may include low serum cholesterol and triglycerides\(^1\text{-}^{10}\). There is hardly any study available showing pathological and biochemical correlation (of SGPT and liver biopsy reports) in malaria.

Routine liver biopsy in patients of malaria with jaundice is unethical as it never helps in the diagnosis or management of the patients. It takes longer time than examination of blood film, rapid diagnosis tests, or even bone marrow examination. Hence, it cannot be advocated as a diagnostic tool for acute malaria. Liver function tests are of value to a limited extent (as mentioned before). When SGPT is excessively elevated, one should search and exclude concomitant presence of viral hepatitis, leptospirosis, infectious mononucleosis, or dengue. Falling short of this, we suggest that instead of labelling a patient as malarial hepatitis, one should classify it as “malaria with jaundice”.

We hope more high quality work on malaria be pursued and published in times to come.

References