Jaundice in Falciparum Malaria

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OBJECTIVE: a) To determine whether a correlation exists between the total serum bilirubin and the parasite count, and b) to determine if serum bilirubin correlates with certain other parcmeters in falciparum malaria.

DESCRIPTION: Published reports of the prevalence of jaundice in falciparum malaria have varied from one per cent to 72 per cent in a group of 46 fatal cases in Africa. Jaundice was a common feature in therapeutic malaria; e.g., in one series of 400 syphilitics inoculated with malaria, six per cent developed jaundice (1). Apart from jaundice, abnormality of hepatic function in falciparum malaria is common (2). Hepatomegaly can be demonstrated during an acute attack in approximately half the cases of malaria (3); following recovery, the liver returns to its normal size within a few days.

DESCRIPTION: This study was conducted at the Trad Provincial Hospital in Southeast Thailand. Between 11 January 1973 and 21 July 1974 a malaria clinic was operated daily from 8 AM to 9 AM. Patients were self—referred or referred by the hospital doctors. Of 11,241 patients who were screened 4,824 had falciparum malaria and 929 had vivax malaria. The present survey was conducted on all adult (over age 15) patients with malaria seen in the clinic during a 40 day interval. For each patient with malaria, venous blood was used to determine parasite density (except for those with vivax malaria) by the method of Earle and Perez, and the packed cell volume (hematocrit) using a microcapillary centrifuge. On each serum the bilirubin, creatinine, SGPT, and alkaline phosphatase concentrations were measured using an Auto—Analyzer.

PROGRESS: Slight increases in total serum bilirubin (to between 1—2 mg per cent) occurred in 55 per cent of the patients with falciparum and 42 per cent of the patients with vivax malaria (Table 1). However, if jaundice is defined as a total serum bilirubin over 2.0 mg per cent, then it did not occur in any of the 24 patients with vivax malaria. Clinical jaundice is rarely reported in vivax malaria. Of the 236 patients with falciparum malaria and an average parasite count of 26,000 per cu.mm., 19 per cent had jaundice. Depth of jaundice (as defined above) correlated ($r=0.35$, $p<0.01$) with the parasite count (Table 2), as it occurred in only 5 per cent of the patients with a parasite density below 1,000 per cu.mm. but in 45 per cent of those with a count over 100,000 (Table 1).

The serum bilirubin correlated positively with serum alkaline phosphatase, SGPT, serum creatinine, parasite density and negatively with the packed cell volume. The serum alkaline phosphatase correlated with SGPT, serum bilirubin and parasite density. The SGPT only correlated with serum alkaline phosphatase and serum bilirubin.

In most patients recovery from jaundice was rapid and coincided with successful treatment with quinine of the falciparum malaria. For example, in one patient the total serum bilirubin was 8.0 mg per cent on admission but had decreased to 0.9 mg per cent five days later. The severity of malaria tended to be less in the older patients as shown by the negative correlation between age and parasite count ($r=-0.19$, $p<0.05$).

There was an inverse correlation between the total serum bilirubin and the hematocrit ($r=-0.295$, $p<0.01$); however, not all of the jaundiced patients were anemic. Anemia was more common in the seriously ill patients; as the hematocrit correlated inversely with the parasite count ($r=0.322$, $p<0.001$).

DISCUSSION: There have been few studies using the direct (and accurate) method for counting malaria parasites in patients with naturally acquired falciparum malaria. Thus, it is not surprising that this is the first study to show a correlation between the parasite count and the total serum bilirubin. This supports the strong clinical impression that jaundice is more common in patients seriously ill with falciparum malaria.

We found a correlation between anemia and jaundice which confirms that hemolysis is one factor in the etiology of jaundice in malaria. The serum bilirubin also correlated with the other indices of hepatic function (SGPT and alkaline phosphatase) which suggests that the jaundice is at least partly due to liver damage. Thus, the production of excess bilirubin is the result of excessive hemolysis but the failure of its removal from the blood may be due to liver damage (4). Besides the SGPT and the alkaline phosphatase, the serum bilirubin also correlated with the serum creatinine, the parasite count, and the packed cell volume. Thus, the serum bilirubin seems to be the most useful index of hepatic function in falciparum malaria, and is also a useful guideline to estimate the severity of the disease.

Table 1. Total Serum Bilirubin (mg per cent) vs Parasite Count in 236 Patients with Falciparum Malaria*

Falciparum Range of Parasite Count (per cu. mm.)	Patients with Bilirubin >1.0 mg%	Patients with Bilirubin >2.0 mg%	Mean Bilirubin (± SEM)**	Range
0–99	24% (4/17)	6% (1/17)	0.90 ± 0.14	0.4–2.9
100–999	38% (8/21)	5% (1/21)	0.93 ± 0.10	0.3–2.1
1000–9999	47% (31/66)	17% (11/66)	1.27 ± 0.10	0.4–4.9
10000–99999	59% (60/101)	17% (17/101)	1.61 ± 0.17	0.5–12.0
100000+	87% (27/31)	45% (14/31)	3.56 ± 0.84	0.4–20.6
Average 26000	55% (130/236)	19% (44/236)		
Patients with Vivax Malaria	42% (10/24)	0% (0/24)	0.99 ± 0.06	0.4–1.7

* Includes data on 24 patients with vivax malaria

** Standard error of the mean

Ross (5) reported that quinine therapy sometimes induced an increase in the serum bilirubin level. But we found that reduction of the parasite density by quinine is usually associated with a rapid reduction in the serum bilirubin concentration.

We did not find jaundice in our 24 patients with vivax malaria (nor in others that we have studied), although jaundice in vivax malaria has been reported by some workers. It is probably rare in pure infections with *P. vivax;* this indicates the importance of accurate species identification.

SUMMARY: Jaundice (defined as a total serum bilirubin over 2 mg per cent) occurred in 19 per cent (44/236) of a group of patients with falciparum malaria and an average parasite density of 26,000

asexual parasites per cu.mm. The serum bilirubin correlated positively with the parasite density ($p < 0.01$) and inversely with the packed cell volume ($p < 0.01$); this confirms that the jaundice is at least partly due to hemolysis. The serum bilirubin also correlated positively with the SGPT and the serum alkaline phosphatase levels, which indicates that hepatic damage also contributes to the jaundice. The prevalence of jaundice varied from 6 per cent in patients with a parasite count less than 1,000 per cu.mm. to 45 per cent in patients with a parasite count over 100,000. Jaundice was not present in any of 24 patients with vivax malaria.

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Table 2. Intercorrelations of Seven Parameters in 236 Patients with Falciparum Malaria*

Parameters	Age	Parasite Count	Hematocrit	Bilirubin	SGPT	Alk Phos	Creatinine
Age	1.0	−0.19	0.157	0.008	−0.044	−0.032	0.03
Parasite Count		1.0	−0.322	0.352	0.151	0.230	0.205
Hematocrit			1.0	−0.295	−0.007	−0.169	−0.158
Bilirubin				1.0	0.351	0.274	0.226
SGPT						0.340	0.094
Alk Phos						1.0	0.052
Creatinine							1.0

* With $n = 236$ the following values of r are associated with the listed probability levels:

r	p
> 0.296	< 0.001
> 0.225	< 0.01
> 0.18	< 0.05