RESEARCH REPORT

HIDDEN *PLASMODIUM FALCIPARUM* INFECTIONS

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Abstract. Mixed infecion of *P. vivax* and *P. falciaprum* malaria frequently recorded in field survey. However mixed infection was frequently misdiagnosed as single infection due to low parasite density, difficult species identification and procedure error of microscopic examination. Our previous report showed high rates (32-33%) of *P. vivax* infection following treatment of previously assumed to be only P. *falciparum* infection. In a study of 992 patients with initial presentation with *P. falciaprum*, we found that 104 (10.5%) of patients had *P. falciparum* appearing during 28 days in the hospital (ranged 1-28 days) following chloroquine treatment for *P. vivax*. The potential for *P. falciparum* appearing following elimination of *P. vivax* must be considered in malaria treatment.

P. vivax and *P. falciparum* are the most widespread and commonly studied of the four human malaria species, and mixed infections of the two are frequently recorded in field surveys (McKenzie and Bossert, 1997). Nevertheless, misdiagnosis of mixed infections as single infections may result from low parasite density, difficulty in species differentiation, and procedural errors of microscopic examination. Recent field studies using acridine orange, nested PCR, and microtiter-plate hybridization have indicated that mixed infections are far more prevalent than previously recorded (Zhou *et al*, 1998). Clinical studies have found high rates of *P. vivax* infection (32-33%) following treatment of patients previously assumed to be infected only with *P. falciparum* (Looareesuwan *et al*, 1987). Here we report a high rate of "hidden" *P. falciparum* infections that appeared following chloroquine treatment for *P. vivax*.

The study was conducted between April 1992 and December 1997 at the Bangkok Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. Patients older than 12 years were enrolled in the study if they had acute vivax malaria upon admission, had not received antimalarial treatment before admission, had no patent *P. falciparum* upon admission and signed a consent form. All patients were treated with a standard regimen of 1,500 mg chloroquine (CQ) over 3 days.

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Overall, 992 patients were enrolled in the study. Of these 10.5% (104) experienced appearance of *P. falciparum* during the 28 days in the hospital. Time of *P. falciparum* appearance varied from 1 day to 28 days following commencement of CQ treatment for *P. vivax* (mean=12.6 days; SD= 6.82). Table 1 gives a summary of clinical and laboratory characteristics of the two groups. Measurements found to be significantly different between the two outcome groups were: *P. vivax* parasitemia on admission ($p<0.0001$), packed cell volume ($p<0.0001$), albumin ($p<0.0001$), globulin ($p<0.0001$), and alkaline phosphatase ($p<0.0001$), suggesting these may be used as indicators of mixed infection with *P. falciparum* undetected by microscopic examination.

Conducting this study in a hospital setting where malaria cannot be transmitted allowed us to eliminate the possibility that the *P. falciparum* appearance is due to a new infection. As *P. falciparum* is first patent usually 9-10 days following infection, a *P. falciparum*- infected mosquito bite immediately prior to admission cannot account for the majority of cases in which the parasites appeared over 10 days following chloroquine administration. Although it is possible that later appearances may be due to heterogeneity in either the host immune response or the parasites themselves, we think it is unlikely that over half the parasites examined have such widely variant pre-patent periods. Instead, the evidence for parasite interaction described above suggests that *P. falciparum* is chloroquine-resistant and that its appearance is directly related to the treatment for *P. vivax*. This follows the findings of neurosyphilis malariatherapy studies (Boyd *et al*, 1938) which suggested interspecific suppression between *P.*

falciparum and *P. vivax*. More recently, mathematical models of mefloquine treatment of mixed *P. vivax*-mefloquine-resistant-*P. falciparum* infections indicated a surge in *P. falciparum* parasite density following the removal of *P. vivax* (and thus non- and cross- specific immunity raised by *P. vivax*) (Mason and McKenzie, 1999).

P. falciparum liberation from a non- and cross-specific immune response raised by *P. vivax* remains a hypothesis, and a more detailed model of conditions leading to subdetectable *P. falciparum* levels and the effect of chloroquine treatment is being developed. Nevertheless, given the severity of *P. falciparum* malaria, the potential for *P. falciparum* appearing following elimination of *P. vivax* must be considered. Patients should be warned to report any reappearance of fever, and follow-up blood checks are highly indicated. The question of whether all *P. vivax*-positive patients should be treated for *P. falciparum* as well remains a controversial hypothesis and awaits similar studies in other regions.

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