Subacute Clinical Forms of Plasmodium falciparum Malaria in Travelers Receiving Chloroquine-Proguanil Prophylaxis

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We have observed 4 French travelers, returning from African countries, who were not immune to malaria and were receiving chloroquine-proguanil prophylaxis, in whom the diagnosis of malaria could easily have been missed because the clinical signs were uncommon. These cases suggest that chloroquine-proguanil prophylaxis is not always effective and that travelers with unexplained symptoms should be monitored closely for malaria.

In France, the antimalarial chemoprophylaxis recommended for travelers to countries with a low rate of chloroquine resistance is a combination of 100 mg of chloroquine base and 200 mg of proguanil daily, from the day of departure until 4 weeks after return [1]. However, the efficacy of such chemoprophylaxis has not been clearly evaluated, and the consequences on the clinical presentation of malaria are unknown.

We have observed 4 nonimmune travelers returning from African countries and receiving chloroquine-proguanil prophylaxis, in whom the diagnosis of malaria could easily have been missed because the clinical signs were uncommon. In these 4 patients, malaria did not induce high fever and was revealed only by intermittent low-grade fever, fatigue, vasomotor flushing, chills, diarrhea, headache, and/or hepatomegaly (table 1). Diagnosis was based only on systematic and repeated blood smears. The 4 patients reported good adherence to the prophylactic regimen, although we did not assess blood levels of chloroquine or proguanil.

These cases suggest that chloroquine-proguanil prophylaxis is not always effective in countries with a low rate of chloroquine resistance. These cases are most likely related to chloroquine and proguanil resistance in Plasmodium falciparum, but we were not able to perform antimalarial drug-sensitivit tests because of the low parasitemia.

Furthermore, chloroquine-proguanil prophylaxis can lead to atypical forms of malaria and to negative blood smears (thin film rather than thick smear), markedly hindering the diagnosis. Similarly subacute cases of Plasmodium falciparum malaria were described >10 years ago in patients taking chloroquine prophylaxis, at a time when chloroquine resistance was starting to emerge [2, 3]. Likewise, prior chemoprophylaxis with chloroquine and/or proguanil led to a reduction in the severity of falciparum malaria in patients at the London Hospital for Tropical Diseases during the period 1987–1991 [4].

The difficulties for diagnosis of malaria in cases of chloroquine-proguanil prophylaxis have been raised in pediatric and adult patients living in areas of endemicity [5]. These difficulties are related to the subpatent low parasitemia observed in patients receiving suboptimal chemoprophylaxis. Diagnosis difficulties due to low parasitemia are not overcome by new techniques, such as acridine orange staining (QBC test [Becton Dickinson]) or HRP2 antigen detection (ParaSight TM-F test, ICT Malaria Pf test), because of a lack of sensitivity in patients with low parasitemia. These techniques have not been used in the 4 patients described here. Nonetheless, in our experience, the detection level for parasitemia has been estimated at 5 parasites/μL for thick smears and 10 parasites/μL for acridine orange staining [6].

Numerous studies have shown that the sensitivity of HRP2 antigen detection was below that of thick smears in patients with low parasitemia. For example, in a study of travelers with malaria, all false-negative results with the ParaSight TM-F test and 2 of the 3 false-negative results with the ICT malaria Pf test occurred in samples with <100 parasites/μL [7]. In another study, the sensitivity of the ParaSight TM-F test has been shown to decrease from 93%, for parasitemia >100 parasites/μL, to 89%, for parasitemia of 50–100 parasites/μL, down to 40%, for parasitemia <50 parasites/μL [8]. The best way to detect subpatent parasitemia is by PCR, a technique considered to be 100–1000 times more sensitive than microscopy [7, 9]. As these patients have a less severe disease, appropriate antimalarial therapy may await either positive results of PCR or serology or the occurrence of detectable parasitemia after the interruption of chemoprophylaxis.

In conclusion, patients receiving chloroquine-proguanil pro-
Table 1. Clinical and biological features of subacute Plasmodium falciparum malaria in 4 French travelers receiving chloroquine-proguanil prophylaxis.

<table>
<thead>
<tr>
<th>Patient’s age (y), sex</th>
<th>Country or countries visited</th>
<th>Day of onset of symptoms</th>
<th>Clinical manifestations</th>
<th>Biological signs</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>28, M</td>
<td>Senegal</td>
<td>8</td>
<td>Nocturnal fever, mild diarrhea</td>
<td>Leukopenia, thrombocytopenia, hepatic cytolysis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Negative blood smears&lt;sup&gt;a&lt;/sup&gt; on days 8 and 9 after return; positive thick smear on day 13 (2 trophozoites/µL)</td>
</tr>
<tr>
<td>39, M</td>
<td>Senegal</td>
<td>11</td>
<td>Fever from last day of travel until hospitalization, then no fever, hepatomegaly</td>
<td>Thrombocytopenia, hepatic cytolysis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 negative blood smears from day 11 to day 15 after return; positive thin film on day 26 (0.2% parasitemia)</td>
</tr>
<tr>
<td>77, F</td>
<td>South Africa</td>
<td>2</td>
<td>Headache, flushes and chills, no fever</td>
<td>None</td>
<td>Negative thin film on day 2 after return but positive thick smear (1 trophozoite/µL)</td>
</tr>
<tr>
<td>26, F</td>
<td>Mali, Senegal</td>
<td>10</td>
<td>Diarrhea, then nausea and vomiting, no fever</td>
<td>Mononucleosis syndrome</td>
<td>Negative thin film on day 10 after return but positive thick smear (1 trophozoite/2µL)</td>
</tr>
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</table>

<sup>a</sup> Included both thin- and thick-film smears.<br><sup>b</sup> Blood transaminases >1.5 and <5 times the normal value.

Phylaxis who have unexplained symptoms should be monitored closely for malaria. Above all, blood smears with thick films for Plasmodium research should be repeated, if negative, and carefully examined.

References