Prolonged Plasmodium falciparum Infection in Immigrants, Paris

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Few immigrant travelers have Plasmodium falciparum infections >2 months after leaving malaria-endemic areas. We conducted a case–control study to identify factors associated with prolonged P. falciparum infection in immigrant travelers. Results suggest that P. falciparum infection should be systematically suspected, even months after travel, especially in pregnant women and first-arrival immigrants.

Approximately 100 countries endemic for malaria are visited by 125 million international travelers yearly, and >30,000 contract imported malaria (1). In France, the number of imported cases of Plasmodium falciparum malaria was estimated to be 4,500 in 2004, with a median time of 10 days between departure from an area endemic for malaria and diagnosis (2). The duration of a P. falciparum infection in humans is generally believed not to exceed 12 months. Most epidemiologic studies show that few patients have malaria onset >2 months after returning from travel (3,4). Late occurrence of infection could have severe consequences if physicians do not relate symptoms suggestive of malaria to travel history. Another risk is transfusion-transmitted malaria from an asymptomatic carrier of P. falciparum trophozoites (5).

Cases of late occurrence of P. falciparum malaria have been reported (6–9), but risk factors are unknown. The objective of this study was to determine the incidence and identify factors associated with prolonged P. falciparum infection in immigrant travelers.

The Study

A case–control study was conducted among patients with P. falciparum malaria diagnosed at Bichat-Claude Bernard and Saint-Denis Hospitals in Paris, France. Many African immigrants come to these hospitals. Participants traveled to or lived in an area endemic for malaria and had a P. falciparum infection during 1996–2005. The diagnostic criterion was P. falciparum trophozoites on a blood smear confirmed by the Centre National de Reference du Paludisme (CNRP) in Paris, without epidemiologic evidence of autochthonous, transfusion-transmitted, or occupational malaria. Case-patients had P. falciparum infections detected >59 days after their arrival in France. Controls had P. falciparum infections detected ≤30 days after their arrival. For each case-patient, 4 controls were matched by calendar year and hospital of diagnosis (70 cases and 280 controls). Data were collected from the CNRP database in which all cases are prospectively included and medical records are checked. We only considered immigrants (persons born in an area endemic for malaria and residing in France), which resulted in 61 case-patients and 197 controls. We distinguished first-arrival immigrants (persons who emigrated to France and never returned to areas endemic for malaria) from visiting friends and immigrant relatives (persons who traveled back to areas endemic for malaria after immigration to France).

Logistic regression was used to identify factors associated with prolonged P. falciparum infection and estimate odds ratios (ORs) and 95% confidence intervals (CIs). For multivariate analysis, variables with p values <0.25 were introduced into the model and removed after a backward stepwise approach, which resulted in only values with p<0.05 in the final model (except for age groups). Statistical analysis was performed by using Stata software version 8.2 (Stata Corporation, College Station, TX, USA).

During the 10-year period, 61 (2.3%) late infections occurred among 2,680 diagnosed P. falciparum malaria infections. The median diagnosis delay was 5 months (interquartile range 3–9 months). These infections included 10 patients (5 pregnant women, 2 HIV-positive patients, and 3 first-arrival immigrants) with clinical malaria >1 year after their arrival. Four of them, all pregnant women, had clinical malaria >3 years after their arrival. For the case–control study, 197 controls were compared with 61 case-patients (Figure). Table 1 shows the main characteristics of case-patients and controls. Case-patients were younger (median age 30.6 years vs. 34.5 years, p = 0.04) and more often female (54.1% vs. 38.1%, p = 0.03) than controls. The mean parasitemia level was lower for case-patients than for controls (0.6% vs. 1.4%, p = 0.04), including patients with 8 asymptomatic cases versus none of the controls (in these cases, diagnosis of malaria was made through systematic checking).

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Among immigrant travelers, 3 groups had a higher risk for prolonged *P. falciparum* infection: pregnant women, first-arrival immigrants, and HIV-positive patients. A total of 27.9% (n = 17) of the patients were pregnant women, with a median (range) age of 22 (16–36) years. All were of African origin and had become pregnant in France; 10 (58.8%) were in their second trimester, 5 (29.4%) were in their third trimester. First-arrival immigrants were younger than other patients (mean age 26.2 vs. 37.6 years, p = 0.001). All patients were of African origin except for 1 Indian man.

| Variable                      | Case-patients (n = 61), no. (%) | Controls (n = 197), no. (%) | OR (95% CI) | p value |
|-------------------------------|---------------------------------|------------------------------|-------------|---------|
| **Sex**                       |                                 |                              |             |         |
| Female                        | 33 (54.1)                       | 75 (38.1)                    | 1           |         |
| Male                          | 28 (45.9)                       | 122 (61.9)                   | 0.52 (0.29–0.93) | 0.03   |
| **Age, y**                    |                                 |                              |             |         |
| <5                            | 2 (3.3)                         | 10 (5.1)                     | 1           |         |
| 5–14                          | 5 (8.2)                         | 18 (9.1)                     | 1.39 (0.22–8.51) | 0.83   |
| 15–60                         | 53 (86.9)                       | 163 (82.7)                   | 1.63 (0.34–7.66) | 0.83   |
| >60                           | 1 (1.6)                         | 6 (3.1)                      | 0.83 (0.06–11.23) |         |
| **Origin**                    |                                 |                              |             |         |
| Sub-Saharan Africa            | 55 (90.2)                       | 181 (91.9)                   | 1           |         |
| Comoros Islands               | 5 (8.2)                         | 14 (7.1)                     | 1.18 (0.41–3.41) | 0.89   |
| Other                         | 1 (1.6)                         | 2 (1)                        | 1.65 (0.15–18.5) |         |
| South America                 | 0                               | 1 (0.5)                      | NA          |         |
| Caribbean                     | 0                               | 1 (0.5)                      | NA          |         |
| India                         | 1 (1.6)                         | 0                             | NA          |         |
| **First-arrival immigrant**   |                                 |                              |             |         |
| No                            | 24 (39.3)                       | 183 (92.9)                   | 1           |         |
| Yes                           | 37 (60.7)                       | 14 (7.1)                     | 20.15 (9.54–42.57) | <0.001 |
| **Region of malaria acquisition** |                              |                              |             |         |
| West Africa                   | 32 (52.5)                       | 132 (67)                     | 1           |         |
| Central Africa                | 22 (36.1)                       | 44 (22.3)                    | 2.06 (1.09–3.92) | 0.03   |
| East Africa                   | 1 (1.6)                         | 2 (1)                        | 2.06 (0.18–23.46) |         |
| Comoros Islands               | 5 (8.2)                         | 18 (9.1)                     | 1.15 (0.4–3.32) |         |
| Other                         | 1 (1.6)                         | 1 (0.5)                      | 4.12 (0.25–67.74) |         |
| **Chemoprophylaxis**          |                                 |                              |             |         |
| No                            | 50 (82)                         | 118 (59.9)                   | 1           |         |
| Yes                           | 9 (14.8)                        | 71 (36)                      | 0.3 (0.14–0.65) | 0.002  |
| Unknown                       | 2 (3.2)                         | 8 (4.1)                      | NA          |         |
| **Prophylaxis with mefloquine** |                              |                              |             |         |
| No                            | 56 (91.8)                       | 186 (94.4)                   | 1           |         |
| Yes                           | 3 (4.9)                         | 3 (1.5)                      | 3.32 (0.65–16.92) | 0.15   |
| Unknown                       | 2 (3.3)                         | 8 (4.1)                      | NA          |         |
| **Antimalarial self-medication** |                              |                              |             |         |
| No                            | 55 (90.2)                       | 171 (86.8)                   | 1           |         |
| Yes                           | 5 (8.2)                         | 15 (7.6)                     | 1.04 (0.36–2.98) | 0.95   |
| Unknown                       | 1 (1.6)                         | 11 (5.6)                     | NA          |         |
| Men                           | 28 (45.9)                       | 122 (61.9)                   | 1           |         |
| Nonpregnant women             | 16 (26.2)                       | 69 (35)                      | 1.01 (0.51–2) |         |
| Pregnant women                | 17 (27.9)                       | 6 (3.1)                      | 12.35 (4.46–34.14) | <0.001 |
| **HIV status**                |                                 |                              |             |         |
| Negative                      | 22 (36.1)                       | 42 (21.3)                    | 1           |         |
| Positive                      | 12 (19.7)                       | 6 (3.1)                      | 3.82 (1.26–11.56) | 0.02   |
| Unknown                       | 27 (44.3)                       | 149 (75.6)                   | NA          |         |
| **Symptomatic malaria**       |                                 |                              |             |         |
| No                            | 8 (13.1)                        | 0 (0)                        | 1           |         |
| Yes                           | 53 (86.9)                       | 197 (100)                    | 0.3 (0.25–0.47) | <0.001 |
| **Parasitemia**†              |                                 |                              |             |         |
| High                          | 2 (3.3)                         | 18 (9.1)                     | 1           |         |
| Low                           | 59 (96.7)                       | 179 (90.9)                   | 1.61 (0.53–4.9) | 0.4    |

†Parasitemia (parasitized erythrocytes) was considered high if ≥4% and low if <4% by World Health Organization criteria.

*OR, odds ratio; CI, confidence interval; NA, not applicable.*
HIV infection was associated with prolonged infection, but HIV status was not introduced into the final model because of missing data. Although chemoprophylaxis with chloroquine-proguanil was less common among case-patients than controls (8.5% vs. 21.2%, p = 0.03), the reverse was seen, although not significantly, with mefloquine use (4.9% vs. 1.5%, p = 0.15). Multivariate analysis (Table 2) showed that factors positively and independently associated with prolonged Plasmodium falciparum infection in immigrant travelers were being a first-arrival immigrant (OR 22.93, 95% CI 9.74–53.96, p<0.001), being a pregnant woman (OR 4.21, 95% CI 1.13–15.77, p = 0.03), and mefloquine prophylaxis (OR 11.55, 95% CI 2.06–64.78, p<0.005).

We also observed cases of malaria in a 26-year-old Caucasian man and a 2-year-old African girl who were hospitalized with diagnosis delays of 221 days and 127 days, respectively. The man was a French expatriate who lived in Madagascar for 2 years and took regular chloroquine-proguanil prophylaxis. He was hospitalized 7 months after his return with severe Plasmodium falciparum malaria (impaired consciousness) and responded to treatment. The girl had traveled in Mali for 2 weeks and took regular chloroquine-proguanil prophylaxis. She was hospitalized 4 months after her return with uncomplicated Plasmodium falciparum malaria occurring concomitantly with a Salmonella spp. infection that had been treated 1 week earlier with ceftriaxone.

### Table 2. Factors independently associated with prolonged Plasmodium falciparum infection in 248 immigrant travelers

| Variable                           | OR (95% CI)       | p value |
|------------------------------------|-------------------|---------|
| Age, y                             |                   |         |
| <5                                 | 1                 |         |
| 5–14                               | 1.45 (0.15–13.74) |         |
| 15–60                              | 1.72 (0.25–12)    |         |
| >60                                | 3.04 (0.16–56.25) | 0.45    |
| First-arrival immigrant             |                   |         |
| No                                 | 1                 |         |
| Yes                                | 22.93 (9.74–53.96)| <0.001  |
| Men                                | 1                 |         |
| Nonpregnant women                  | 0.67 (0.28–1.59)  |         |
| Pregnant women                     | 4.21 (1.13–15.77) | 0.03    |
| Use mefloquine                     |                   |         |
| No                                 | 1                 |         |
| Yes                                | 11.55 (2.06–64.78)| 0.005   |

*OR, odds ratio; CI, confidence interval.

Conclusions

Three independent factors were positively associated with prolonged Plasmodium falciparum infection: being a first-arrival immigrant, being a pregnant woman, and taking mefloquine prophylaxis. This study also highlights the risk for blood transfusion-transmitted malaria, a rare but serious complication. Mungai et al. (15) reported 32 cases of transfusion-transmitted Plasmodium falciparum malaria in the United States during 1963–1999 (mortality rate 18.8%). Current US guidelines recommend obtaining a thorough travel history and deferring blood donation if potential donors have emigrated from areas endemic for malaria in the preceding 3 years. However, this measure may not prevent transmission if Plasmodium falciparum is present for >3 years (as in 4 pregnant women in our study). In France, systematic serologic analysis for Plasmodium spp. in blood donors born in areas endemic for malaria was implemented in 2002 (5).

Our findings suggest that physicians should consider the risk for prolonged Plasmodium falciparum infection in immigrant travelers to be higher than usual.
pregnant women and first-arrival immigrants even without recent travel to a country endemic for malaria. The prevalence of asymptomatic \(P. falciparum\) carriers in France or other northern countries is unknown but could be high with the increase in immigration. Public health authorities should be aware of the risk these persons represent for blood donations.

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**etymologia**

*Candida* ([kan′-di-də]), from the Latin—*candidus* (glowing white)

A genus of yeastlike Fungi Imperfecti (for which no sexual reproductive stage is known) of the family *Cryptococcaceae* that produce yeast cells, mycelia, pseudomycelia, and blastospores. When grown in the laboratory, *Candida* appears as large, round, white or cream colonies on agar plates. *C. albicans* infection (or thrush) features distinctive white mouth lesions; “albicans” means becoming white. *C. dubliniensis*, first identified in 1995 at the University of Dublin, is an opportunistic pathogen that can cause both superficial and invasive infections, particularly in the immunocompromised.

*Source:* Dorland’s illustrated medical dictionary. 30th ed. Philadelphia: Saunders; 2003; Sullivan, DJ, Westermeng TJ, Haynes KA, Bennett DE, Coleman DC. *Candida dubliniensis* sp. nov.: phenotypic and molecular characterisation of a novel species associated with oral candidosis in HIV-infected individuals. Microbiology 1995;141:1507–12.