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Prevalence and risk factors associated to pruritus in *Plasmodium vivax* patients using chloroquine in the Brazilian Amazon

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ABSTRACT

Chloroquine-induced pruritus has been described as a common adverse event in African patients being treated for *Plasmodium falciparum* malaria, and has been associated with treatment discontinuation in this setting. In Latin America, where *Plasmodium vivax* is the most common species causing malaria and chloroquine is still used as the first-line schizonticidal for treating this parasite infection, there are no reports on chloroquine-induced pruritus. This study aimed to estimate the frequency of pruritus and associated risk factors in *P. vivax*-infected patients treated with chloroquine in a reference centre in the Brazilian Amazon. In this cross-sectional study, patients who were prescribed with chloroquine for the treatment of microscopy-confirmed *P. vivax* infection in the past five days were actively asked about the occurrence of any level of pruritus and potential risk factors were investigated. Univariable and multivariable logistic regression was performed for the analysis of possible risk factors in two sets of patients: (1) all the patients interviewed and (2) restricted to patients with previous use of chloroquine. Among the 510 patients interviewed, 20.4% (95%CI: 16.9–23.9%) developed any level of pruritus during treatment with chloroquine. Most episodes of pruritus occurred during the first two days of treatment and the most common location was hands and feet. In multivariate analysis performed in the entire population, the only risk factors independently associated to pruritus were allergy history (adjusted odds ratio [AOR]: 1.83; 95%CI 1.02–3.31; $p = 0.044$) and high parasitaemia (AOR: 1.96: 95%CI 1.22–3.13; $p = 0.005$). In the analysis restricted to the 215 patients with previous use of chloroquine, previous chloroquine-induced pruritus was a strong predictor of pruritus occurrence (AOR: 11.84: 95%CI 3.15–44.47; $p < 0.001$). Two patients (0.4%) interrupted treatment due to the severity of pruritus. Pruritus is a common adverse event in patients being treated with chloroquine for *P. vivax* malaria in the Brazilian Amazon. Host–parasite interaction may play a relevant role in the development of pruritus and concurs with the finding of strong association of pruritus with high parasitaemia and allergy history. Patients with previous chloroquine-induced pruritus had a high risk for developing pruritus. Due to its high frequency, this side effect cannot be neglected as it can have major implications on patients' compliance to treatment hampering elimination efforts in the region.

1. Introduction

Although there have been increasing reports of *Plasmodium vivax* resistance to chloroquine, especially in the Pacific region (Baird, 2009), leading some countries to adopt artemisinin-combination therapies (ACTs) as first-line treatment for vivax malaria (Douglas et al., 2010), chloroquine remains recommended as the first-line schizontocidal therapy for *P. vivax* infection in most of the endemic countries (Douglas et al., 2010; Pukrittayakamee et al., 2004). The characteristics that contribute to chloroquine impressive longevity, occupying a central role in the antimalarial arsenal for more than 60 years, are its fast parasite clearance time, prolonged half-life, favourable safety profile and low costs (Baird, 2009; Pukrittayakamee et al., 2004).

Pruritus and gastrointestinal symptoms are the most common side effects during chloroquine use for uncomplicated malaria (Taylor and White, 2004). Although considered a minor adverse

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event, itching associated to chloroquine can cause great discomfort leading eventually to lack of compliance to treatment (Aghahowa et al., 2010). The frequency of chloroquine-associated pruritus has a marked variation, being reported to be as high as 64% in some African populations during treatment for *Plasmodium falciparum* (Mnyika and Kihamia, 1991) and practically insignificant in Thailand, with only 1.9% incidence in patients being treated for *P. vivax* infection (Bussaratid et al., 2000). Several factors have been associated with the risk of chloroquine-pruritus occurrence, such as degree of skin pigmentation (Aghahowa et al., 2010), use for treatment instead of prophylaxis (Gama et al., 2009) and parasite density (Adebayo et al., 1997).

Although in the last decades the main use of chloroquine has been vivax malaria treatment, there is a scarcity of studies measuring the occurrence of chloroquine-induced pruritus in *P. vivax* infected patients (Bussaratid et al., 2000), especially in the Americas, where more than 70% of malaria episodes are caused by this parasite (WHO, 2011), further demonstrating the neglected status of the care around this species infection (Carlton et al., 2011). *P. vivax* terminal therapy requires a course of 7–14-days of primaquine (Price et al., 2011), what emphasizes the importance of measuring the occurrence of pruritus as it can influence patients' adherence to therapy, which is of paramount importance in a context of renewed commitment of the international community with malaria eradication (Alonso et al., 2011).

Brazil responds for around 50–60% of reported cases of malaria in the Americas (WHO, 2011) and *P. vivax* is responsible for more than 80% of malaria episodes (Oliveira-Ferreira et al., 2010). Despite reports of increasing resistance of this parasite to chloroquine (de Santana Filho et al., 2007), the Brazilian National Malaria Treatment Guidelines still recommends the use of chloroquine (10 mg/kg on day 1 and 7.5 mg/kg on days 2 and 3) and primaquine (0.5 mg/kg per day during 7 days) for the treatment of *P. vivax* infection (Brasil. Ministério da Saúde, 2010). The aim of this study was to describe the frequency of chloroquine-induced pruritus and to investigate associated risk factors in patients being treated for *P. vivax* infection, in a reference centre in Brazilian Amazon.

2. Methods

2.1. Study site

The *Fundação de Medicina Tropical Dr. Heitor Vieira Dourado* (FMT-HVD) is a tertiary care centre for Infectious Diseases. Located in the city of Manaus, in the Western Brazilian Amazon, it is responsible for the diagnosis and treatment of around 4130 cases of malaria per year, of which more than 90% are caused by *P. vivax* (Sistema de Informações Operacionais e Epidemiológicas – Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, 2012). Patients systematically return between the third and the seventh day of treatment for assessment of parasite clearance and adverse events. This survey was conducted in 2008, during which the treatment protocol at FMT-HVD consisted in patients being prescribed chloroquine (25 mg/kg over three days) immediately after *P. vivax* microscopical diagnosis and receiving primaquine tablets (0.5 mg/kg/day during seven days) only in the fifth day of treatment, this allowed for assessing adverse events associated solely with chloroquine use.

2.2. Study procedures

This study consisted in interviewing patients above 4 years of age (due to the ability to consistently report itching symptoms) treated for vivax malaria with chloroquine. The interviews were performed in a period between 1 and 5 days after chloroquine completion. Demographic data and clinical malaria data were collected from patients' registries (date of birth, gender, self-reported race, date of malaria diagnosis and date of malaria treatment initiation) and the patients were asked by only two *a priori* calibrated interviewers about previous malaria episodes, previous exposure to malaria, history of allergy and the occurrence of pruritus after initiation of treatment. Episodes of itching occurring up to four days after chloroquine use were classified as chloroquine-induced pruritus. If the patient reported the occurrence of pruritus, specific questions related to this symptom were performed, which included date of presentation after chloroquine initiation, localization of pruritus, requirement of symptomatic treatment (such as anti-histamines or corticosteroids) and interruption of antimalarial treatment due to pruritus. Patients referring pruritus prior to chloroquine initiation were excluded of the study.

2.3. Statistical analysis

A minimum sample size of 500 patients was calculated in order to detect a 7.5% frequency of pruritus, with 95% confidence interval precision of 4% and 80% power. Patients' characteristics were described in terms of proportions. Age was categorized in three age groups: 4–15 years-old, 16–50 years-old, and above 50. Logistic regression was performed in order to evaluate the association of risk factors for the development of pruritus during use of chloroquine for vivax malaria. The analyses were performed with two different sets of patients, the first one including all the interviewed patients and the second restricted to the patients with previous use of chloroquine in which previous malaria and previous use of chloroquine were not evaluated. Initially, a univariable analysis was performed where the association of each variable with pruritus was examined using logistic regression. No variable was *a priori* included in the multivariable analysis. All variable with a $p > 0.10$ were considered for inclusion through a manual forward stepwise variable selection process in a multivariable logistic regression analysis. Variables were included in the model in order of odds ratio (OR) magnitude and the decision to maintain a variable in the final model was based on obtaining a significance level $p < 0.05$ in the likelihood ratio test. All statistical analyses were performed using Stata® version 11.2 (StataCorp®, College Station, TX).

3. Results

3.1. Population characteristics

During the study period, 510 patients under chloroquine use for *P. vivax* treatment at the FMT-HVD were interviewed, of which 59.7% were male, 8.8% were younger than 15 years-old, 68.5% were between 16 and 50 years and 22.7% were older than 50 years of age. Race was not used in the analyses as more than 90% of the study population were of brown skin pigmentation, which reflects the high admixture pattern characteristics of the local population. For 275 patients (53.8%) that was the first episode of malaria and 42.8% reported having used chloroquine for malaria treatment before, with 6.54% of them referring previous occurrence of pruritus.

3.2. Pruritus frequency and clinical characteristics

Pruritus during use of chloroquine for *P. vivax* treatment was reported by 104 patients, determining a frequency of 20.4% (95%CI: 16.9–23.9%). The characteristics of the episodes of pruritus are described in Table 1. All episodes of pruritus initiated during the three days of chloroquine use, with the majority (51.9%) appearing in the second day of treatment. Feet and hands were the main places of pruritus location, accounting together for more than 70% of episodes, followed by generalized pruritus (20.4%) and in the

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