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Short Communication

Decreased uric acid levels in the acute phase of *Plasmodium vivax* malaria

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Abstract

Introduction: Uric acid is one of the compounds associated with the inflammatory process in malaria. It acts as an indicator of cellular damage by activating the immune response and inflammatory process. **Methods:** We measured serum concentrations of uric acid in 60 symptomatic patients before and after treatment for malarial infections caused by *Plasmodium vivax*. **Results:** Lower serum concentrations of uric acid were found during the acute phase of *P. vivax* malaria compared to those in its convalescent phase ($p < 0.0001$). **Conclusions:** Patients in the acute phase of malaria had lower uric acid levels than those in its convalescent phase.

Keywords: Malaria. Uric acid. Acute phase. Convalescent phase.

The inflammatory response in malaria is an important aspect in the pathogenesis of this disease. For many years, the focus of malaria research was heavily concentrated on *Plasmodium falciparum*, which caused a delay in the evolution of knowledge regarding the *Plasmodium vivax* infection. In Brazil, until the 1960s, malaria cases were predominantly caused by *P. falciparum*; however, *P. vivax* has been responsible for 80% of the cases reported in the recent decades. Little is known about the pathophysiology of *P. vivax* malaria or the main contributors in its inflammatory process. The inflammatory process not only leads to death of the parasites, but also induces tissue damage (including dysfunction and endothelial activation) and exhibits signs of worsening during its prognosis. One of the compounds associated with the inflammatory process in *P. falciparum* malaria is uric acid[1].

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Uric acid is the end product of inosine and guanosine metabolism. Inosine and guanosine are phosphorylated to form hypoxanthine and guanine, respectively. Xanthine oxidase, an enzyme present in large amounts in the liver and intestinal mucosa, oxidizes hypoxanthine which subsequently produces xanthine; the latter produces uric acid. Alternatively, the enzyme guanine deaminase catalyzes the conversion of guanine to xanthine, with subsequent oxidation to uric acid. In *P. falciparum* malaria, the increase in uric acid levels is mainly due to the release of hypoxanthine from infected erythrocytes, which is converted to uric acid by the action of enzymes present in the extracellular environment. Additionally, uric acid may get precipitated in the erythrocytes infected with the plasmodia[2].

Uric acid produced or precipitated from the erythrocytes acts as an indicator of cellular damage and activates components of the immune response and inflammatory process[3]. *In vitro* assays conducted on mononuclear cell cultures of erythrocytes infected by *P. falciparum* showed an accumulation of uric acid derived from the hypoxanthine present in the erythrocytes[2]. Additionally, clinical studies have shown increased levels of uric acid in the plasma of patients with severe *P. falciparum* malaria and high-parasitemia[4,5]. Uric acid also exhibits antioxidant activity and provides defense against free radicals by chelating free iron and copper. Uric acid may improve the endothelial function of

smokers and individuals with type 1 diabetes[6]. Knowledge about the pathogenesis, inflammatory response and oxidative stress induced during *P. vivax* infections is still scarce but may prove to be helpful in the treatment of patients with vivax malaria. Determining the uric acid levels may serve as an indicator of the antioxidant status and inflammatory response in patients with *P. vivax* malaria and help to define its relationship with the course and complications of the disease. Thus, we evaluated the serum levels of uric acid in patients infected with *P. vivax* before and after the antimalarial treatment and correlated these values with other laboratory parameters.

In this exploratory study, we investigated the serum uric acid concentrations of patients before and after antimalarial treatment at the Julio Müller University Hospital (HUJM) located in the city of Cuiabá, Mato Grosso, Brazil. HUJM provides a referral service for the diagnosis and treatment of malaria in patients from the south and southwest regions of the Brazilian Legal Amazon. Participation in the study was voluntary. All participants (or their legal guardians, if participants were younger than 18 years of age) signed an informed consent form. The study was approved by the Research Ethics Committee of the Júlio Muller University Hospital (registry CEP 130/HUJM/2011).

The study included 60 symptomatic patients who presented themselves at the HUJM from March 2012 to January 2014 and returned after treatment for further diagnostic evaluation. Patients with *P. vivax* monoinfections were eligible for the study, which were confirmed by thick blood smear microscopy and the polymerase chain reaction. After diagnostic confirmation, the patients underwent clinical examinations along with hematological and blood biochemical evaluations. They also received the recommended treatment for malaria according to the Brazilian Ministry of Health guidelines.

Hematological evaluation of the patients was performed using a multi-parameter hematology analyzer (Pentra 80; Horiba Medical, Montpellier, France). Serum biochemistry was analyzed by a photometric method using a BT-3000 PLUS automated biochemical analyzer (Diamond Diagnostics, Cambridge, MA, USA). Levels of uric acid in the serum were detected using the Uricostat enzimatic AA kit (Wiener, Rosario, Argentina) with a detection limit of 0.03 mg/dL. All patients were advised to return between the 4th and 28th day post-treatment for clinical reevaluation and new parasitological, hematological, and biochemical examinations. Thus, each patient was evaluated twice—once in the acute phase and again in the convalescent phase of the disease.

The Shapiro-Wilk test was used to verify the normality assumption for the distribution of biochemical and hematological parameters. For parameters with normal distributions, a Student's paired t-test was performed. A non-parametric Wilcoxon signed-rank test was applied for parameters with non-normal distributions. The tests were used to compare the distribution of biochemical and hematological parameters in the acute and convalescent phases of the disease. Differences in the values with $p < 0.05$ were considered to be significant for all analyses.

Of the 60 patients enrolled in the study, 47 (78.3%) were men and 13 (21.7%) were women. The ages of the patients ranged from 5 to 76 years, with a median age of 45.0 years (interquartile range: 29.5–55.0 years). The mean time of return for the clinical re-evaluation was 9.4 days, and ranged from 4 to 28 days.

Axillary temperatures, C reactive protein concentrations, and total bilirubin levels were higher in patients during the acute phase of malaria compared to those in the convalescent phase ($p < 0.0001$ for all three conditions). However, the total leukocyte counts ($p < 0.0001$), total proteins ($p < 0.0001$), albumin concentration ($p = 0.0006$), and platelet counts ($p < 0.001$) were lower in the acute phase compared to those in the convalescent phase. In the same way, uric acid levels were lower ($p < 0.0001$) in the acute phase compared to those in the convalescent phase (**Table 1, Figure 1**).

In our study, lower concentrations of uric acid in the plasma were observed in patients during the acute phase of *P. vivax* malaria. To our knowledge, no studies have shown the dynamics of uric acid production in the inflammatory response caused by *P. vivax*. In malaria caused by *P. falciparum*, xanthine and hypoxanthine accumulate within the parasitized erythrocytes and are released into the bloodstream upon rupture during release of the schizonts, thereby increasing the uric acid levels and triggering an inflammatory response mediated by dendritic and mononuclear cells[2]. In malaria caused by *P. falciparum*, increased uric acid levels have been correlated with severity of the disease and the production of various cytokines such as interleukin-6 and tumor necrosis factor-α[4]. Contrarily, our results showed lower levels of uric acid among patients in the acute phase of *P. vivax* malaria. Similarly, Araujo *et al*. (2008)[7] reported that lower, but nonsignificant, levels of uric acid were present among patients with thrombocytopenia in the acute phase of *P. vivax* infection.

Uric acid is an important component of the inflammatory process, acting as a pro-inflammatory flag that induces the production of free radicals[3]. Uric acid can still act as a marker of endothelial dysfunction where it decreases the production of nitric oxide by lowering the availability of arginine to the endothelial cells[8]. However, it also can act as a potent plasma antioxidant[9]. In fact, uric acid is the most important substance with antioxidant properties found in the plasma[10]. Increased values of uric acid in the serum have been associated with an improved clinical evolution of several pathologies such as sarcoma[11] and chronic obstructive pulmonary disease[12]. Conversely, uric acid levels (along with platelet counts) were reported to be lower in patients with neonatal sepsis than in the healthy controls[13]. Another study has also shown that uric acid levels are lower in patients with sepsis than those in healthy individuals[14]. Moreover, the uric acid levels in newborns with fatal sepsis were found to be lower than those who survived the sepsis[14].

These findings corroborate with our results that, in patients with *P. vivax* malaria, clinical improvement due to antimalarial treatment was associated with an increase in the uric acid levels. In fact, another study has shown that oxidative stress is involved in the pathophysiology of *P. vivax* malaria[15]. Thus, a decrease in the uric acid levels during the acute phase of the disease may be a negative finding in *P. vivax* malaria.

TABLE 1: Clinical and laboratory characteristics of the patients included in the study before (acute phase) and after antimalarial treatment (convalescent phase).

Characteristics	Acute phase (n=60)	Convalescent phase (n=60)	P value*
Age (years) Median (1st–3rd quartile)	45.0 (29.5-55.0)		-
Time clinical reevaluation (days) Mean (standard deviation)	9.4 (5.7)		-
Parasitemia (parasites/µL) Median (1st–3rd quartile)	4,000 (1,300-11,500)		-
Hemoglobin[a] (g/dL)	13.2 (11.9-14.3)	13.0 (11.8-14.3)	0.068
Hematocrit[a] (%)	38.5 (35.7-42.7)	38.6 (34.8-41.9)	0.447
Total leukocytes[b] (leukocytes /µL)	5,150 (4,325-6,305)	6,700 (5732-7,700)	<0.0001*
Total bilirrubin[b] (mg/dL)	1.0 (0.6-1.7)	0.5 (0.3-0.6)	<0.0001*
Urea[b] (mg/dL)	29.0 (24.3-37.8)	26.0 (21.0-33.0)	0.007
Creatinine[b] (mg/dL)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	1.000
Aspartate aminotransferase[b] (U/L)	26.0 (20.0-35.0)	22.5 (18.3-31.0)	0.027
Alanine aminotransferase[b] (U/L)	31.5 (21.3-44.5)	33.0 (18.3-54.0)	0.248
Axillary temperature[b] (°C)	36.6 (36.0-37.7)	36.0 (35.6-36.2)	<0.0001*
Platelets[b] (platelets/µL)	104,500 (67,650-175,00)	263,500 (230,000-354,500)	<0.0001*
C reactive protein[b] (mg/dL)	73.9 (39.6-112.3)	6.7 (3.9-9.4)	<0.0001*
Total proteins[a] (g/dL)	6.7 (0.6)	7.2 (0.5)	<0.0001*
Albumin[b] (g/dL)	3.90 (3.60-4.20)	4.10 (3.80-4.30)	0.0006*
Uric acid[a] (mg/dL)	4.5 (1.16)	5.2 (1.3)	<0.0001*

[a]Means e standard deviation – Students paired t-test; [b]Median (1st–3rd quartile) – Wilcoxon rank test. * Statistically significant values

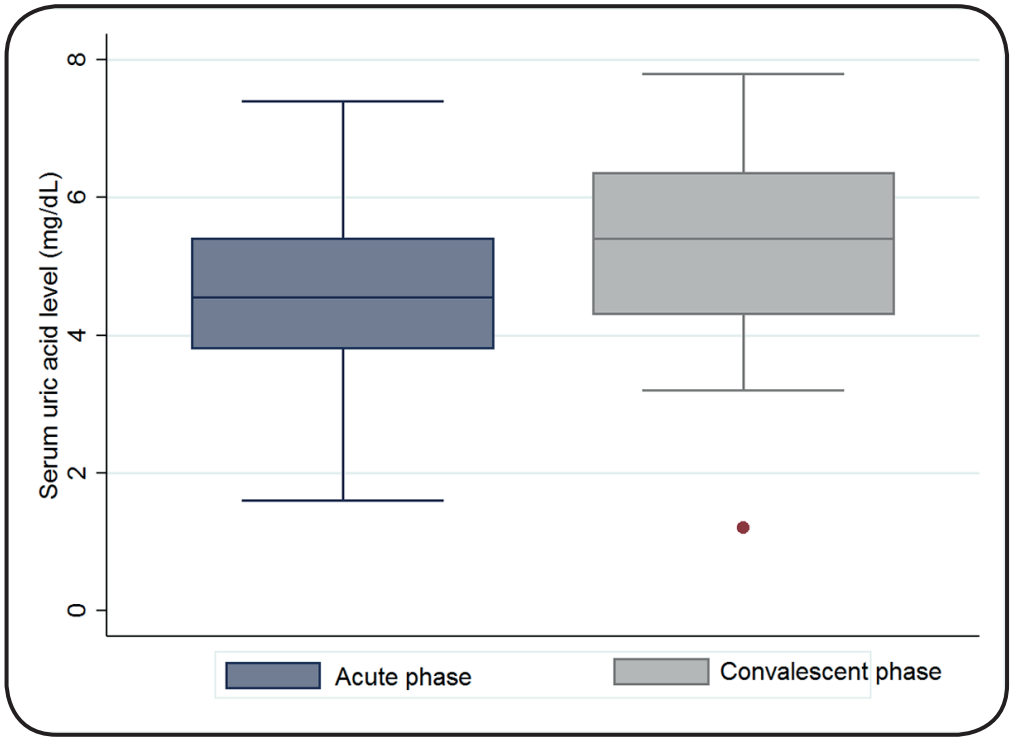

FIGURE 1: Serum uric acid levels in the acute and convalescent phases of *Plasmodium vivax* malaria.

In our study, patients with *P. vivax* malaria had lower uric acid levels in the acute phase than in the convalescent phase. Routine uric acid evaluations in patients with *P. vivax* malaria may indicate the antioxidant capacity of the plasma and provide additional information for the their treatment. Further studies should be performed to evaluate the role of uric acid in the pathogenesis of *P. vivax* malaria and to determine the potential benefits of using this marker in the prognostic evaluation of patients.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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