Rev. Inst. Med. trop. S. Paulo
45(1):29-34, January-February, 2003

CLINICAL AND LABORATORY FINDINGS OF *Plasmodium vivax* MALARIA IN COLOMBIA, 2001

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SUMMARY

A descriptive study was carried out in 104 patients with *Plasmodium vivax* malaria, from the region of Turbo (Antioquia, Colombia). Clinical features and levels of hemoglobin, glycemia, serum bilirubin, alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), creatinine and complete blood cell profile were established. 65% of the studied individuals were men and their mean age was 23. Of all individuals 59% had lived in the region for > 1 year and 91% were resident in the rural area. 42% were farmers and 35% had a history of malaria. The mean parasitaemia was 5865 parasites/mm^3. The evolution of the disease was short (average of 4.0 days). Fever, headache and chills were observed simultaneously in 91% of the cases while the most frequent signs were palmar pallor (46%), jaundice (15%), hepatomegaly (17%), and spleen enlargement (12%). Anemia was found in 39% of the women and in 51% of the men, 8% of individuals had thrombocytopaenia and 41% had hypoglycemia.

KEYWORDS: *Plasmodium vivax;* Clinical; Laboratory; Non-complicated; Malaria.

INTRODUCTION

Plasmodium vivax is the most commonly human malaria parasite of the four species affecting humans. Currently, this infection is endemic in many countries of Asia, South Pacific, North Africa, Middle East and South and Central America[15]. A significant increase on the number of cases was observed during the period 1990-1999[26] reaching a total of 896000 *P. vivax* cases reported in America in 1999.

In Colombia, a total of 70938 cases of malaria were diagnosed in 1999, of which 65% were *P. vivax* malaria[8]. In the region of Antioquia, 21009 cases of malaria were reported in 1999, of which 82% were *P. vivax* malaria. Within this region, the municipality of Turbo reported 3409 cases of malaria (81% *P. vivax*)[2].

The most commonly described clinical presentation of *P. vivax* malaria is fever, headache, chills and sweating. Some authors have made occasional reports of abdominal and osteomuscular pain, vomiting, diarrhea, hepatomegaly and splenomegaly[19,33]. Symptoms and clinical signs of the infection caused by *P. vivax* resemble infection caused by other species[13,33] and none of the symptoms can predict a diagnosis of malaria or differentiate the infecting species, as it has been proposed in cases of infection in children in low endemic areas[18].

There has been an increase in the number of reports of complications during *P. vivax* infection, including cerebral malaria and seizures[31,32], pulmonary edema[9,23,28], respiratory distress syndrome[5], kidney failure[1], and death[4,16]. In Colombia, cases of acute respiratory distress syndrome and death have been reported in the last few years[22] as well as cerebral malaria, thrombocytopaenia, severe anemia and kidney, liver and lung damage[11].

As may be noted in these works, in the last few years the presence of clinical complications caused by *P. vivax* has been reported and we have received field reports of deaths caused by this species, we also ignore its clinical and laboratorial behavior. A retrospective study carried out by us[11] confirms that there are no recent clinical studies about the behavior of *P. vivax* in Colombia and we proposed the present work with the aim of elucidating the profile of complications that are produced in a high number of patients and to design strategies for the Ministry of Health in its treatment.

MATERIALS AND METHODS

Sample selection: The descriptive longitudinal study was carried out in patients with *P. vivax* malaria, in the municipality of Turbo (Antioquia, Colombia). The sample was constituted by patients being attended to at the local hospital from February to March, 2001. They were included in the study as they attended to at the malaria diagnosis facility; men and women were selected according to the inclusion criteria. The protocol was approved by the ethical commission of the University of Antioquia.

The size of the sample was calculated based on the following equation[21]:

$$n = \frac{N \times Z^2 \times p \times (1-p)}{\left(N \times e^2\right) + \left(Z^2 \times p \times (1-p)\right)} \quad \Rightarrow \quad n = \frac{4589 \times 1.96^2 \times 0.5 \times (0.5)}{\left(4589 \times 0.1^2\right) + \left(1.96^2 \times 0.5 \times (0.5)\right)} = 94$$

Financial support: Universidad de Antioquia.
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Where: n = sample size; N = population total, i.e., cases of *P. vivax* malaria in 2000 in Turbo; p = proportion of *P. vivax* malaria presenting a specific symptom or sign; e = sampling error; Z = confidence level.

Considering 10% losses, a total 104 patients were included in the study.

Malaria diagnosis: Diagnosis, species and number of parasites were determined by Giemsa stained thick blood smears following WHO recommendations[17].

Clinical evaluation: After the diagnosis, anamnesis and clinical evaluation were done by a physician who followed a previously designed protocol and recorded the information in a designed form. The evaluation included body weight, assessment of blood pressure, heart and respiratory rates, axillary's temperature, systems examination and description of the general condition of the patient.

Laboratory tests: At the enrollment in the study and regardless of the fasting period, 12 ml of venous blood was obtained from each patient. The level of Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), direct and indirect bilirubin, creatinine, glycemia and complete blood cell profile were assessed. Normal reference values of hemoglobin were based on the Wintrobe´s criteria[27] with some modifications introduced by us.

Inclusion criteria: All the following had fulfilled: a. >1 year age; b. *P. vivax* unique infection; c. Permanent residence in the study area; d. History of fever during the present episode; e. Informed consent (signed by the patient or his/her parents if underage).

Exclusion criteria: To have at least one of the following: a. Severe undernourishment; b. Pregnancy; c. Febrile disease associated; d. History of antimalarial drug intake during the present disease.

Statistical analysis: The programs EpiInfo 6.04 and Stat-Graphics 3.1 were used. The following analyses were carried out:

a) Evaluation of the association of two non-metric variables with the chi square test (X^2) i.e.: appearance/absence of a syndrome and its relation with sex or age group; anemia (yes or not) and occupation.

b) Comparison of average between independent groups using the Kruskal and Wallis H test (non parametric anova) i.e.: parasitaemia and age group, bilirubin or enzyme ALT or AST and jaundice (yes or not).

c) Simple lineal correlation of metric variables, i.e.: hemoglobin in parasitaemia; enzymes ALT or AST in parasitaemia; bilirubin in enzymes ALT or AST.

RESULTS

104 ambulatory patients were studied with *P. vivax* diagnosis. Age fluctuated between 2 and 75 years old, with 23.2 average (Medium = 20.0). 32 patients were children (< 15 years old), 22 of them (69%) were male, 72 were adults and 46 of them (64%) were male. All patients lived in Turbo, 91% in rural areas and the time of residence in 41% was ≤ 12 months. 42% carried out agricultural works and during the past year 35% had malaria (72% *P. vivax* and 28% *P. falciparum*).

The average body weight of children was 24.9 kg (SD 10.4) and of adults 59.5 kg (SD 15.0), no gender differences were observed in both groups ($p > 0.10$). In children, the correlation coefficient between weight and age was 0.84. Mean parasitaemia was 5865 parasites/mm^3 (SD 6307). The evolution time of the disease from the start of the symptoms to the moment of clinical evaluation was from 1 to 22 days (average = 5 days, SD 4.2 days; 95% CI: 4.1 to 6.1 days).

Main symptoms observed during the clinical disease are shown in Table 1. 91% of the patients had from 5 to 7 symptoms and the most frequent were: fever (99%), headache (99%) and chills (91%). This triad was positive in 91% of the patients. During the clinical examination, 98% of the patients were fully alert and 2% lethargic, 65% had normal temperature (< 37.5 °C). Mean values of their vital signs are indicated in Table 2. Palpable liver and spleen were presented simultaneously in 7% and a significant association between these two signs was established ($p < 0.0000$).

Table 1
Symptoms and clinical signs at any stage of the illness in 104 patients with *P. vivax* malaria

	Number of patients	%
Symptoms		
Fever	103	99
Headache	103	99
Chills	95	91
Sweating	81	78
Osteomuscular pain	60	58
Vomit	41	39
Abdominal pain	35	34
Dizziness	34	33
Diarrhea	14	13
Signs		
Hand pallor	48	46
Jaundice	16	15
Liver enlargement	18	17
Spleen enlargement	10	10

Table 2
Vital signs at the medical evaluation in 104 out-patients with *P. vivax* malaria (1)

Sign (2)	Mean	DE	C. I.
Hearth rate	97	22	93.3 – 113.4
Respiratory rate	27	11	24.3 – 27.7
Diastolic pressure	66	12.4	63.9 – 69.2
Systolic pressure	111	12.8	108.3 – 113.9
Arterial mean pressure	81	11.5	78.9 – 83.9
Temperature	37.6	1.2	37.4 – 37.8

(1) mean: arithmetic mean; SD: standard deviation; CI: 95% mean confidence interval; (2) Hearth and respiratory rates by minute; arterial blood pressure: Hg mm.; temperature °C

Mean parasitaemia in patients exhibiting 1-4 symptoms was 3371 (SD ± 3504) parasites/mm^3, for patients with 5-7 symptoms it was 5776 (SD ± 6425) and for patients with 8-10 symptoms it was 8675 (± 6298).

Laboratory findings are shown in Tables 3, 4, and 5. We observed high levels of direct bilirubin in 6% of the patients and high indirect bilirubin in 20% of them.

Glycemia was < 55mg/dL in 31% (11/35) of females, and > 105mg/dL in 11% (4/35) of them. 47% of the men (31/66) presented lower values than the threshold and 17% (11/66) above. In total 41% of the patients were hypoglycemic and 15% hyperglycemic. Hypoglycemia affected equally men and women, children and adults and was not associated to specific clinical manifestations ($p > 0.05$). Mean glycemia values in hypoglycemic individuals was significantly different ($p < 0.0001$) from values in the rest of the individuals (44.8 and 79.5 mg/dL respectively). Glycemia levels were independent from parasitaemia,

Table 3
Laboratory results in 102 out-patients with malaria by *P. vivax* (1)

Item	$\bar{X} \pm SD$	CI	Reference value
Glycemia (mg /dL) in women	79.7 ± 38	67.0 – 93.4	65 – 105
Glycemia in men	83.0 ± 41	73.0 – 92.9	75 – 110
Platelets (10^3/mm^3)	269 ± 85	252.2 – 285.7	130 – 400
Erythrocytes (10^6/mm^3)	4.5 ± 1.1	4.3 – 4.8	4.7 – 6.1
Leukocytes (10^3/mm^3)	6.2 ± 2.5	5.7 – 6.7	4.8 –10.8
Lymphocytes (%)	32.8 ± 12.8	30.4 – 35.4	20.5 – 51.1
Neutrophils (%)	57 ± 13	54.8 – 59.9	42.2 – 75.2
Monocytes (%)	4 ± 2.7	3.6 – 4.7	1.7 – 9.3
Eosinophils (%)	3 ± 2.9	2.91 – 4.0	2.0 – 5.0
Parasitaemia	5865 ± 6307	4653 –7077	—

(1) mean: arithmetic mean; SD: standard deviation; CI: 95% mean confidence interval.

Table 4
Sex and age hemoglobin values (g/dL) in 104 outpatients with malaria by *P. vivax* (1)

Age	No.	Hemoglobin $\bar{X} \pm SD$	CI	Anemia No. (%)	Reference value (lower value)
Women					
2-6	3	10.3 ± 1.9	8.1 – 12.4	2 (66)	11.5
7-12	5	11.5 ± 1.2	10.5 – 12.5	2 (40)	11.5
13-18	9	12.3 ± 1.3	11.4 – 13.1	4 (44)	12.0
>18	19	13.9 ± 4.0	12.2 – 15.6	6 (32)	12.0
Men					
2-6	2	9.4 ± 1.0	8.2 – 10.6	2 (100)	11.5
7-12	17	12.1 ± 4.6	9.9 – 14.2	11 (65)	11.5
13-18	8	12.6 ± 1.9	10.2 – 15.0	5 (62)	12.5
>18	40	14.1 ± 3.5	13.0 – 15.2	16 (40)	13.0

(1) Mean arithmetic mean; SD: standard deviation; CI: 95% mean confidence interval.

Table 5
Age and sex bilirubin (mg/dL), creatinine (mg/dL), ALT and AST (UI/L) values in 104 outpatients with malaria by *P. vivax* (1)

Item	$\bar{X} \pm SD$	CI	Reference value(2)
Direct bilirubin (mg/dL)	0.24 ± 0.13	0.21 – 0.26	0.00–0.30
Indirect bilirubin (mg/dL)	0.78 ± 0.48	0.69 – 0.88	0.00–1.10

Women	1-10 years		>11 years	
Item	$\bar{X} \pm D.S.$	CI	$\bar{X} \pm D.S.$	CI
Creatinine	0.5 ± 0.82	0.370 – 0.63	0.79 ± 0.12	0.745 – 0.83
AST	46 ± 14.76	19.50 – 66.49	34 ± 17.82	27.49 – 40.56
ALT	24 ± 5.12	16.09 – 32.40	26.5 ± 12.8	21.81 – 31.21

Men	1-10 years		11-14 years		>15 years	
Item	$\bar{X} \pm D.S.$	CI	$\bar{X} \pm D.S.$	CI	$\bar{X} \pm D.S.$	CI
Creatinine	0.54 ± 0.09	0.48 – 0.59	0.68 ± 0.135	0.56 – 0.81	0.94 ± 0.30	0.86 – 1.03
AST	35.9 ± 19.09	24.9 – 6.9	29.4 ± 7.2	22.7 – 36.1	38.3 ± 19.6	32.4 – 44.1
ALT	24.9 ± 11.5	18.3 – 31.6	24.7 ± 8.6	16.8 – 32.7	25.0 ± 7.6	22.8 – 27.3

(1) Mean arithmetic mean; SD: standard deviation; CI: 95% mean confidence interval; (2) Reference values:

Women:	1-10 years	>10 years	Men:	1-10 years	10-14 years	> 14 years
Creatinine	0.5-0.9	0.7-1.2		0.5-0.8	0.6-1.0	0.8-1.5
ALT	10-35	9-52		10-35	10-55	21-72
AST	15-40	10-30		15-40	15-40	17-59

number of days of the disease, hemoglobin, systolic and mean arterial blood pressure ($r < 0.15$ and $p > 0.05$). However, the age of the patients was slightly correlated with hypoglycemia ($r = 0.30$; $p > 0.05$).

Creatinine and ALT levels were normal in all individuals. AST levels were high in 36% of the women over 10 years of age and in 30% of the men under 11 years old.

Anemia was observed in 34 males and 14 females and in all cases the frequency of anemia was inversely correlated with age (Table 4). According to age groups, hemoglobin mean values exhibited important differences, in women (KW = 7.007; df = 3; p = 0.071664) and in men (KW = 14.439; df = 3; p = 0.002365). There were not significant differences among male and female hemoglobin values within each age group ($p > 0.05$). In children, anemia was neither associated to sex, occupation nor malaria antecedents ($p > 0.05$). There is a very slight correlation between the hemoglobin level and time of residence in the area ($r = -0.13$), age ($r = 0.37$) and parasitaemia ($r = 0.40$).

The platelet average was 269000/mm^3. Thrombocytopaenia was present in 8 adult patients (8%), with mean hemoglobin of 15 g/dL and a mean parasitaemia 6170/mm^3; hepatomegaly was present in 3 and hepatoesplenomegaly in one case.

The white cell count was abnormal in 34% of the patients: 29% leucopenia and 5% leucocytosis; the average of leukocytes was of 6200/mm3. The lymphocytopenia, neutropenia, monocytopenia and eosinopenia prevailed on their respective excess conditions, being in 17%, 13%, 16% and 30% of the cases. Eosinopenia and eosinophilia were the most common alterations (30% and 19% respectively).

DISCUSSION

91% of the patients lived in rural areas; the population was highly exposed to malaria considering the annual parasite index (API) of 30.5 per thousand observed during 1999, estimated over 111578 residents[7]. 35% of the patients had a history of malaria infection during the previous year. The period of evolution of the disease was relatively short (average: 5 days).

The triad fever, headache and chills, was present in 91% of the patients. This confirms previous observations made by us in Antioquia, Colombia[11] and, it also agrees with classic findings[13,33] and with recent studies made by several authors in different geographic regions (Brazil[10], India[6,12], Thailand [18], Saudi Arabia[19], Gambia[24], Singapore[25], Australia[29]) who also reported the presence of splenomegaly, hepatomegaly and anemia as the most common signs in vivax malaria.

The frequency of vomiting was age-dependent and was between 15% and 67% in the above mentioned studies. A frequency of this symptom in 48% of individuals was reported in Saudi Arabia[19], while in Gambia[24] it was 67%. In these two studies carried out in children under five years old, the presence of vomiting was the second most common symptom. Children under 14 year-old from Pará-Brazil[10] had a frequency of 24%. In our study we observed 50% frequency of vomiting in children and 35% in adults. Furthermore, in the present study the frequency of diarrhea was 12.5% in children, which is in accordance with other authors who reported 13% frequency in children from Pará-Brazil[10].

No statistically significant difference was observed among parasitaemia and number of symptoms maybe due to the reduced size in two of the three compared groups (KW = 5.766, g l = 2, p = 0.055971).

The frequency of clinical signs was significantly lower than the frequency of symptoms, which confirms what is already well known. It has been reported that patients with acute non-complicated malaria have few abnormal physical signs, including a mild anemia and a palpable spleen[33]. However, besides the high fever, signs such as pallor, coluric urine, hepatomegaly, splenomegaly, thrombocytopaenia and low hemoglobin were present in 18% to 64% of the patients in the cited studies and were predominant in children. In our study, hepatomegaly and splenomegaly were present in 17% and 10% respectively and the latter was more frequent in children (22%), significantly different between children and adults (Fisher's exact test, p = 0.0093496). However, differences have been observed concerning other findings in children under 15 years old. While in Brazil[10], splenomegaly was detected in 46% of the children, in Surat-India[6] 13% were positive and in Shoklo-Thailand[18] (2-15 year-old children) 8% of *P. vivax* and 25% of *P. falciparum* infected patients had spleen enlargement. Hepatomegaly was positive in 29% of children patients in Brazil[10], in 4% in Surat[6], in 3% for *P. vivax* and in 13% for *P. falciparum* in Shoklo[18], and in 28% among us. We found hepato-splenomegaly in 16% of 32 children and 3% of 72 adults and there was a significant association in both groups between this finding and malaria (Fisher´s exact test, $p < 0.041$). It is striking the splenomegaly-hepatomegaly ratio observed by us is much lower than the one reported by others (0.8 vs. 1.6 in Surat[6], 2.4 in Shoklo[18], 3.2 in Pará, Brazil[10]), with the exception of Gambia[24] (0.9). Our data confirms a lack of association between hepatomegaly and jaundice ($p > 0.05$) or increased ALT or AST ($p > 0.05$).

Thrombocytopaenia is a common finding in *P. falciparum* and *P. vivax* infections and the cause of it remains unclear[30]. 8% of our patients evidenced this. Previously, we have reported 36% thrombocytopaenia in 281 hospitalized adults with malaria in Medellín, associated in a similar way to *P. vivax* and *P. falciparum*[11]. The presence of thrombocytopaenia is not related to the severity of infection and the association with bleeding or disseminated intravascular coagulation syndrome (DIC) is uncommon[30]. Bleeding (epistaxis and petechiae) was observed in this study in 2 of 8 thrombocytopenic patients, which confirms previous findings[11]. Presence of thrombocytopaenia has been reported in 71% of the malarial cases in Melbourne[29], while in Calcutta HAZRA *et al.*[12], 1998, reported DIC in 3% of *P. falciparum* infected patients but in none by *P. vivax*.

Along with glycemia changes, the most frequent abnormal findings in this study were anemia (39% in women and 51% in men; 69% in children and 56% in adults). In a different study on blood parameters during malaria infection, carried out in El Bagre (Colombia), we found that 30% of 1-14 year-old children and 25% of adults had anemia (febrile non malaria controls were anemic in 10% and 20%, respectively)[3].

Anemia in malaria is due to the destruction of infected erythrocytes and to bone marrow suppression[13,14], but in highly endemic areas malnutrition and intestinal parasite infections (mainly uncinariasis and strongyloidiasis) boost this problem. DA SILVA VENTURA *et al.* (1999), reported 71% of intestinal parasitism in Brazil[10] among 0-14 year-old children with vivax malaria, 19% had ancylostomiasis, and 100% of

those with helminthiasis had anemia. As in general, malnutrition affects more children than adult population, and mainly protein-caloric malnutrition is a widely spread problem in Colombia, we exclude severe undernourished children from the present study. In the studied children we found a high correlation between weight and age (r = 0.84), this together with a clinical examination led us to exclude severe malnutrition. In summary, protein-caloric malnutrition and intestinal parasite infections can not be discarded as the cause of anemia in this study.

In this study, 41% of the patients had hypoglycemia. This is the most common silent finding in African children with severe malaria[20]. In Medellín, we have found glycemia < 61 mg/dL in 3% (n = 291) of hospitalized patients with vivax or falciparum malaria[11]. A total of 41% of the patients with hypoglycemia is high considering that our study was carried out in non-hospitalized and non-complicated patients. Furthermore, this finding is very concerning as it was observed regardless of the fasting period. However, the presence of a hypoglycemic syndrome (headache, sweating and faintness with glycemia < 55 mg/dL) was not observed in any patient.

In conclusion, acute febrile *P. vivax* malaria (in outpatients of the municipality of Turbo, Antioquia), exhibits a mild clinical pattern, where the most frequent sign is the presence of anemia, which is more intense in < 15 year-olds, followed by asymptomatic hypoglycemia. Malnutrition and intestinal parasitism might account for the high frequency of anemia.

RESUMEN

Características clínicas y de laboratorio de la malaria por *Plasmodium vivax,* Colombia 2001

Se realizó un estudio descriptivo con 104 enfermos de malaria por *Plasmodium vivax*, en Turbo (Antioquia, Colombia). Se evaluaron las características clínicas y los niveles de hemoglobina, glicemia, bilirrubina sérica, ALT, AST, creatinina y hemograma completo. Los hombres representaron el 65% del grupo, la edad promedio fue 23 años, el 59% tuvo más de un año de residir en el lugar, el 91% residían en zona rural, el 42% realizaba trabajos agrícolas y el 35% tenía antecedentes de malaria. La parasitemia promedio fue de 5865 parásitos/mm^3. La evolución de la enfermedad fue corta (mediana de 4,0 días). Fiebre, cefalea y escalofrío estuvieron simultáneamente en 91% de los casos y los signos más frecuentes fueron palidez palmar (46%), ictericia (15%), hepatomegalia (17%) y esplenomegalia (12%). La anemia se encontró en el 39% de las mujeres y en el 51% de los hombres, y el 8% presentó trombocitopenia. Los niveles séricos de bilirrubinas directa e indirecta, de enzimas ALT y AST y de creatinina se encontraron, en general, normales. El 41% de los pacientes tuvo hipoglicemia.

ACKNOWLEDGEMENTS

We are very grateful with the University of Antioquia for their financial support, to the community of Turbo for their participation in the study, to directives of the local hospital of Turbo and the operative personnel of malaria for their logistical support, and to Dr. Amanda Maestre for the revision of the translated text.

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Received: 19 June 2002
Accepted: 27 September 2002