Association of severe malaria with ABO-blood group types in an endemic zone of Colombia

Asociación de malaria severa con tipo de grupo sanguíneo ABO
en una zona endémica de Colombia.

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ABSTRACT

Introduction: *malaria is considered one of the most important tropical illnesses in public health causing millions of infections and deaths each year. Many studies have tried to establish an association between the severe form of the disease and the ABO-blood group type. In Colombia, a country with large endemic zones for malaria there are not enough studies or statistic data about this possible association.*

Methods: *a retrospective case-control study of patients with severe and uncomplicated malaria in the endemic zone of Apartadó, Colombia, was performed between January 2000 and June 2006. Only the clinical records with blood group ABO and Rh classification were included.*

Results: *a total sample of 92 patients was obtained: 49 with severe malaria and 43 with uncomplicated malaria. From the total sample, 68.5% were women and the median age of 21.5 years*

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(*min* 1-*max* 80). O*f the patients with diagnosis of severe malaria*, 59.2 % *were women*. T*he more frequent parasite species was* Plasmodium falciparum. S*evere malaria was more frequent among patients classified with blood group* O (65.3 %) *and positive* R*h* (93.9 %), *but this association was not statistically significant.*

Conclusion: *even though severe malaria was more frequent among patients classified with blood group* O *and positive* R*h, an association between blood group and severe malaria could not be established.* T*he controversial association of these variables previously found in other populations could be probably explained by the demographic distribution and characteristics of those.*

KEY WORDS

M*alaria*
ABO *blood* G*roup system*
C*olombia*

RESUMEN

Introducción: la malaria es considerada una de las más importantes enfermedades tropicales en salud pública, causando millones de infecciones y muertes cada año. Muchos estudios han tratado de establecer una asociación entre la forma grave de la enfermedad y la clasificación sanguínea ABO. En Colombia, un país con grandes zonas endémicas de malaria, no existen suficientes estudios y datos estadísticos acerca de esta posible asociación.

Métodos: se realizó un estudio de casos y controles de pacientes con malaria severa y no complicada en la zona endémica de Apartadó, Colombia y ejecutado entre enero de 2000 y junio de 2006. Sólo las historias clínicas con información acerca de la clasificación sanguínea ABO o Rh fueron incluidas.

Resultados: la muestra total fue de 92 pacientes, 49 con malaria grave y 43 con malaria no

complicada. De la muestra total, 68,5% eran mujeres y la edad media de 21,5 años (mínimo 1-máximo 80). De los pacientes con diagnóstico de malaria grave, 59,2 % eran mujeres. El parásito más frecuente fue la especie de P. falciparum. La malaria grave fue mas frecuente entre los pacientes clasificados con grupo sanguíneo O (65,3 %) y Rh positivo (93,9 %), pero esta asociación no fue estadísticamente significativa.

Conclusión: aunque la malaria severa fue mas frecuente en pacientes con grupo sanguíneo O y Rh positivo, una asociación entre la severidad de la malaria y la clasificación sanguínea no pudo ser establecida. La controvertida asociación entre estas variables previamente encontrada en otras poblaciones, probablemente puede ser explicada por la distribución y características demográficas de dichas poblaciones.

PALABRAS CLAVE

M*alaria*
C*lasificación grupo sanguíneo* ABO
C*olombia*

INTRODUCTION

Malaria is considered a worldwide major public health problem (1) as it is the most important parasite disease affecting humans and causing millions of deaths each year (2). In tropical and subtropical regions of the world, it is estimated that malaria is responsible for 300 to 500 millions of infections and 2 to 3 millions of deaths per year (3); being considered as one of the main health problems in regions like Africa, India, Southeast of Asia, and South America (4). Given the optimal environmental conditions for malaria transmission among different territories of Colombia, the country is considered as one of the endemic zones in the world (1,3). In the Co-

lombian zones of Urabá and Bajo Cauca (1998), among the people affected by the disease, the reported parasite species prevalence is 66 % for P. *vivax* and 33 % for P. *falciparum* (1). The latest, is the parasite widely associated with a more severe presentation of the disease (1,2). However, besides the parasite species, the clinical presentation and severity of the disease are influenced by the geographic zone, demographic characteristics and host susceptibility (5).

Many pathophysiological mechanisms have been postulated to explain host susceptibility for parasite colonization and clinical presentation of the disease. Some studies have suggested that host susceptibility could be linked to the ABO-blood group and/or Rh type due to the presence of different erythrocyte receptor systems that act as ligands to facilitate parasite adhesion (6).

Several authors have stated that while groups A, B, and O seem to be equally susceptible to the infection, group AB show less propensity to infections. Additionally, it is suggested that groups A and O exhibit less colonization by P. *falciparum* (7). In a systematic review published in 2007, it was reported that while in 7 different studies a significant association between P. *falciparum* malaria and ABO blood classification was found, this association could not be demonstrated in other seven studies (8). About Rh classification, many studies have found a protective association between negative Rh and the susceptibility to P. *vivax* malaria as this blood group get less infections (9,10).

In terms of the severity of the disease, it has been found that severe malaria frequency is in linear relation with parasite concentration and intra-erythrocyte rosettes formation mainly by P. *falciparum* that invades all type of erythrocytes involving complex physiopathological processes deriving in more severe effects (1,6). P. *falciparum* erythrocyte invasion and rosette formation is believed to be favored by erythrocyte surface antigens among the different ABO-blood group and Duffy types (6). Some studies have found that P. *falciparum* form rosettes with more frequency in those erythrocytes with A and B blood groups, but less frequently in those of group O, which could indicate some resistance of this group to the severe presentation of malaria (8,11-15).

At the epidemiological level and only considering the clinical studies, a clear association between severe malaria and blood group classification has not been established (16). Some comparative studies have demonstrated differences in terms of blood group types and the presence of severe malaria concluding that patients with group O could be more resistant to the infection by P. *falciparum* (14,15). However, other studies have failed to demonstrate this association (16,17). In a recent publication, Cserti and Dzik (2007) suggested that the controversial association between severe malaria and ABO blood groups is closely related to the geographic distribution of the different blood groups among the endemic zones (16). These studies have been performed in many tropical territories affected by malaria around the world, however, in Colombia, a country with large endemic zones; there are no many similar studies or statistic data about this alleged association.

MATERIALS AND METHODS

All the clinical records of hospitalized patients with malaria, in the regional hospital of the Apartadó town, an endemic zone of Urabá (Colombia) during the period of January 2000 and December 2005 were evaluated. The clinical records of patients with malaria and ABO blood group and Rh classification were included. A retrospective case-control study of patients diagnosed with severe malaria and uncomplicated malaria during this period was performed. Neonatal malaria was used as exclusion criteria.

The cases of severe malaria were defined by the presence of one or more of the following crite-

ria based on the report published by the World Health Organization (WHO, 2000) (18) and adapted by the researchers keeping into account the criteria established in Colombia by the Ministry of Social Protection for malaria falciparum parasitemia and severe anemia (2007) (19), and for severe trombocitopenia according to the definition published by Tobon et al. 2006 (20): cerebral malaria (defined as unrousable coma not attributable to any other cause in a patient with falciparum malaria), severe normocytic anaemia (hemoglobin <7.0 mg/dL and hematocrite <20 % -adapted by the researchers-, hypoglycaemia (glucose <40 mg/dL), metabolic acidosis with respiratory distress, fluid and electrolyte disturbances, acute renal failure (creatinin >3.0 mg/dL), acute pulmonary oedema and adult respiratory distress syndrome (ARDS), circulatory collapse, shock, septicaemia, abnormal bleeding, jaundice (total bilirrubin TB >3.0 mg/dL),haemoglobinuria, hyperparasitaemia (>50,000 asexual parasites / μL* -adapted by the researchers-), severe thrombocytopenia (platelets <20.000/μL -adapted by the researchers-).

Information about demographic variables, blood group classification, and parasite type and laboratory tests values was collected from each clinical record of both groups: uncomplicated malaria and severe malaria. Data was processed in the statistic software SPSS 10®. Bivariated analysis to evaluate differences between numeric variables between cases and controls was performed through the U Mann-Whitney test and to evaluate the association between categorical variables a Chi-square test was performed. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A p value <0.05 was set for statistical significance.

RESULTS

A total of 197 clinical records of hospitalized patients with malaria between January 2000 and December 2005 in the Hospital Antonio Roldán Betancur were initially evaluated, of those, 92 records fulfilled the inclusion criteria of having information about ABO or Rh blood classification. The sample was conformed by 49 patients in the group of cases and 43 in the control group. Median age of the total sample was 20 years (interquartile range 5.5-28 years) and 68.5 % (63/92) were women, from these, 46 % (n=29) were in the third trimester of pregnancy. The frequency distribution of the different ABO blood groups of the total sample was: group O (67.4 %), group A (23.9 %) and group AB (8.7 %). In terms of Rh classification, 94.6 % of patients of the total sample were classified as positive. The more frequent parasite in the total sample was P. *vivax* (61.5 %), followed by P. *falciparum* (36.3 %). Mixed malaria by both parasites was present in 2 patients (2.2 %). The demographic and clinical characteristics of patients of cases and control groups are displayed in table 1.

In the group of cases of severe malaria (n=49) the diagnosis was performed by the following criteria: severe anemia 69.4 % (34), ADRS in 22.4 % (11), hyperparasitemia in 16.7 % (8), hepatic failure 14.6 % (7), severe thrombocytopenia in 4.2 % (2), renal failure 2.1 % (1), and cerebral malaria 2.1 % (1). There were no cases diagnosed by severe hypoglycemia. There was one death caused by severe malaria.

The bivariated analysis to establish association between severity of the disease and the ABO and Rh blood group classification did not show statistical significance for any of the blood types.

Table 1. CHARACTERISTICS OF PATIENTS IN THE TWO CLINICAL CATEGORIES CASES-SEVERE MALARIA AND CONTROLS-UNCOMPLICATED MALARIA

	Severe (n=49)	Uncomplicated (n=43)	P value
Age in years	16(3-24)[&]	13(17-32)[&]	0.004*
Sex			
Men	40.8 % (20)	20.9 % (9)	0.068
Women	59.2 % (29)	79.1 % (34)	
Pregnancy	16.3 % (8)	48.8 % (21)	0.000*
Parasite species			
P. Falciparum	53.1 % (26)	16.2 % (7)	0.000*
P. Vivax	44.9 % (22)	79 % (34)	0.001*
P. Falciparum and P.Vivax	2 % (1)	2.4 % (1)	0.053
Clinical parameters			
Hemoglobin mg/dl	6 (5-9.3)[&]	10.4 (8.2-11)[&]	<0.001*
Hematocrite %	17.8 (15.3-27.7)[&]	30.2 (24.9-33.9)[&]	<0.001*
Platelets /μl	108 500 (62500-227 750)[&]	143000 (85 750-240 750)[&]	0.109
Total bilirrubin mg/dl	2.3 (1.6-3.2)[&]	0.7 (0.52-1.15)[&]	0.002*
Blood sugar mg/dl	74 (70.1-88.5)[&]	80.5 (71.5-82.7)[&]	0.697
Parasite count	5 360(1 596-7 800)[&]	1 596 (912-8 160)[&]	0.220

[&] Median and interquartile values

* Statistically significant differences, U-Mann Whitney test

Table 2 displays the calculated OR values with their respective 95 % CI for each of the groups with respect of severity of malaria.

With regard to the association of the rest of variables with the severity of malaria, a statistically significant association between this one and sex was found (OR 2.60, 95 % CI 1.03-6.60; p=0.044) being males 2.6 times more at risk of developing severe malaria than females. Examining the association of the severity of the disease and range of age, it was observed that severe malaria affects significantly more those patients between one and 12 years of age (OR 5.46, 95 % CI 1.78-17.51; p=0.0015). Also, there was significant association with the parasite species being P. *falciparum* as a risk factor (OR 5.65, 95 % CI 1.92-17.21; p=0.0003) and P. *vivax* as a protective factor (OR 0.19, 95 % CI 0.07-0.54; p=0.0004) for developing severe malaria. Pregnancy also presented a significant association with severe malaria (OR 0.24, 95 % CI 0.07-0.77; p=0.006). As in the rest of patients of the sample, in pregnant women, severe malaria did not show significant association with the ABO blood Group classification.

Evaluating parasite species and its possible association with any blood type, it was found that for infection with each of both parasites: P. *falciparum* and P. *vivax*, the most frequent blood type was O (75.8 % for P. *falciparum* and 62.5 % for P. *vivax*) without any significant association between this blood type and parasite species.

Table 2. FREQUENCY DISTRIBUTION OF THE ABO BLOOD GROUPS AND BIVARIATED ANALYSIS IN THE STUDIED CLINICAL CATEGORIES

	Severe	Uncomplicated	OR (95% CI)	P value
ABO groups				
O	65.3% (32)	69.8% (30)	0.81 (0.33-1.96)	0.64
A	22.4% (11)	25.6% (11)	0.84 (0.33-2.19)	0.72
AB	12.2% (6)	4.7% (2)	2.86 (0.54-14.99)	0.19
Rh groups				
Positive	93.9% (43)	95.3% (41)	0.69 (0.11-4.40)	0.70
Negative	6.1% (3)	4.7% (2)		

DISCUSION

Several reports in the literature establish association between the blood classification system ABO and malaria; specifically between group AB and severe malaria and refer that people with blood type O are relatively resistant to develop severe malaria by P. F*aciparum* (8,9,14,15). In the present study, an association between blood group and severe malaria was not found. These findings are similar to what was reported by Montoya *et al*. where no association could be established between the presence of ABO antigens and malaria by P. F*alciparum* or P.*Vivax* in 4 different ethnic groups in Colombia (9). Alike, Cavasin *et al*. found similar frequencies of ABO phenotype between blood donors and malaria patients in 4 areas of Brazilian Amazone (10). In another Amazonic area, Beiguelman *et al*. also failed to find such association arguing that it is probably due to the geographic distribution of the different ABO phenotypes in this region (21). In the present study, 65.3 % of the cases of severe malaria were blood type O, different from what was found by Pathirana et al (15) where the ratio was of 23.8 %; also, in that study, type A was the most frequent (32.5 %) and type B represented 27.5 %. In the present study no cases of severe malaria had blood type B. In uncomplicated malaria patients the predominant blood type was also O, while Pathirana's reported 47.9 % (15). These findings support more the idea that the alleged association between blood type and severity of malaria depends on the demographic distribution and characteristics of the studied population, as every region in the world seems to have different ABO phenotype distribution.

The demographic characteristics of the evaluated population in the present study suggest in general a higher frequency of the disease in women specially those in their third trimester of pregnancy. The bivariated analysis indicated that males are at more risk of developing severe malaria, however, there are not physiopatological mechanisms that could explain this association. This situation could be explained from the public health system point of view, as the strict prenatal assistance and control system of our country assures that women in fertile age and during pregnancy could be detected rapidly in the early phases of the disease avoiding the progression of malaria to a severe stage. Therefore, the ratio of 20 of 29 males affected by severe malaria contrast with the ratio of 29 of 63 females with the same diagnosis probably indicating that even though in this study malaria is more frequent among women, its progress to a severe stage is less frequent in those as well. Another explanation could be the fact that pregnant women with uncomplicated malaria are hospitalized and given special care due to their condition, therefore avoiding complications of their disease (22).

The median age of affected patients by the severe disease was constituted by young adults, but after performing the analysis by groups of age, a high frequency of severe malaria in the age group between 1-12 years was evident. This is possibly due to the susceptibility of children to experience a more severe form of the disease given the poor immunological and nutritional conditions of this population (23-25).

In agreement with the epidemiological data found in our country and previously described in the literature, in the total sample of this study, the most frequent parasite for non complicated malaria found in this endemic zone was P. *vivax*, and for severe malaria was P. *falciparum* being a risk factor for its development as has already been described for many dacades (1,20). Only 2 patients presented mixed infection by P. *falciparum* and P. *vivax*, one of them manifested the severe form of the disease.

The majority of severe cases of malaria were diagnosed by the presence of severe anemia given by highly compromised levels of hemoglobin and hematocrit. This contrast with the results obtained by Tobón et al. (2006) in two Colombian populations, where severe malaria diagnose was more frequently performed by hyerparasitemia and hepatic failure, and less frequently due to severe anemia (20). However, this finding is in agreement with other studies where severe anemia is reported as one of the most frequent parameters for the diagnose of severe malaria in other populations probably due to their geographic conditions (15-17). Coherent also with the reported in the literature, there were not cases of severe malaria diagnosed by severe hypoglycemia (15-17).

CONCLUSION

In the present study, although severe malaria was more frequent among patients classified with blood group O (65.3 %) and positive Rh (93.9 %), an association between blood group and severe malaria could not be established. These findings support more the idea that the alleged association between blood type and severity of malaria depends on the demographic distribution and characteristics of the studied population, as every region in the world seems to have different ABO phenotype distribution.

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