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Impact of ABO Blood Groups and Haemoglobin Variants on the Prevalence of Acute Falciparum Malaria Infection

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Short title: ABO blood groups, haemoglobin variants and malaria

ABSTRACT

Background: There are conflicting reports on the effect of ABO blood type or haemoglobin genotype on the prevalence of falciparum malaria. The present study examined the effects of ABO blood groups and hemoglobin variants on the prevalence of uncomplicated falciparum malaria in Osogbo, Southwestern Nigeria. **Materials and Methods:** A total of 486 malaria positive patients and 486 controls (apparently healthy malaria negative individuals) of age ≥ 16 years were screened for this study. Thick and thin Giemsa-stained blood smears were examined for malaria parasite, ABO blood group antigens tests were performed by standard tube and tile techniques and hemoglobin genotype was determined by cellulose acetate electrophoresis. **Results:** There was no significant relationship between ABO blood groups and malaria (χ^2 = 1.14, df = 3, p = 0.767). However, malaria varied significantly with hemoglobin variants (χ^2 = 27.09, df = 5, p < 0.001). A significant association was observed in the distributions of blood types A, B and O in the malaria group between AA and AS variants only (χ^2 = 7.931, df = 2, p = 0.019). Proportion of malaria infection increases as follows: O+AS (0.345) < B+AS (0.424) < A+AS (0.468) < A+AA (0.489) < B+AA (0.55) < O+AA (0.568). **Conclusion:** This study reveals that when singly considered, malaria infection is influenced by haemoglobin genotype but not by ABO blood type. When combined, O individuals are the most resistant to malaria infection if they are AS but the most susceptible if they are AA.

[Igbeneghu C*, Alabi TT, Adebayo TO, Olisekodiaka MJ, Onuegbu JA, Odaibo AB. **Impact of ABO Blood Groups and Haemoglobin Variants on the Prevalence of Acute Falciparum Malaria Infection.** *Life Sci J* 2022;19(10): 16-20]. ISSN 1097-8135 (print); ISSN 2372-613X (online). http://www.lifesciencesite.com. 03.doi:10.7537/marslsj191022.03.

Keywords: ABO blood groups, Haemoglobin variants, falciparum malaria, prevalence

INTRODUCTION

ABO blood groups and haemoglobin variants have been associated with various diseases including malaria. Many studies have been carried out on the relationship between ABO blood group and mild malaria infection. While some of these studies have reported lack of association between ABO blood group and acute malaria infection (Cavasini *et al.,* 2006; Degarege *et al.,* 2012; Igbeneghu *et al.,* 2014), others have reported significant association between them (Agbonlahor *et al.,* 1993; Beiguelman *et al.,* 2003; Nkon-Akenji *et al.,* 2004). Agbonlahor *et al.* (1993) reported that blood groups O and B male individuals were the most and least susceptible to malaria attack respectively. Beiguelman *et al.* (2003) reported a significant association between individuals with A and/or B antigens and the number of malaria episodes. Nkuo-Akenji et al. (2004) reported that blood group O and group B individuals were the most susceptible and least susceptible to malaria attack respectively. Zerihun *et al*. (2011) reported that blood group A individuals were more susceptible to *P. falciparum* infection compared to blood group O individuals.

With respect to haemoglobin variants, HbAS individuals had been reported to be protected against the frequency of uncomplicated malaria (Williams *et al.,* 2005; Kreuels *et al.,* 2010; Igbeneghu *et al.,* 2015), though some studies had suggested that its greatest impact seemed to protect against either death or severe disease while having less effect on infection per se (Hill *et al.,* 1991; Cooke and Hill, 2001). Similarly, while some studies had reported HbAC individuals to be protected against malaria infection (Modiano *et al.,* 2001; Rihet *et al.,* 2004; Igbeneghu *et al.,* 2015), others had reported lack of protection (Agarwal *et al.,* 2000; Kreuels *et al.,* 2010).

There is little information on the combined effect of ABO blood group and haemoglobin genotype on the prevalence of malaria. It is likely that the ABO blood group and haemoglobin genotype have an effect on the prevalence of uncomplicated malaria. The aim of this study was to investigate the individual and collective effects of these genetic variables on the frequency of malaria in Osogbo, Southwestern Nigeria.

MATERIALS AND METHODS

The study was carried out in Osogbo, Southwestern Nigeria. Participants were drawn from patients attending malaria clinics of Ladoke Akintola University Teaching Hospital and Osun State General Hospital, both in Osogbo, Osun State and apparently healthy individuals who visited these facilities for blood donation and routine investigation.

A total of 972 individuals of age ≥ 16 years participated in this study after clinical examination and informed consent was obtained. The participants comprised 486 individuals with acute malaria and 486 individuals with no clinical signs and symptoms of ill health as of the time of investigation. Ethical approval for this study was obtained from the Joint Ethical committee of Ladoke Akintola University of Technology, Ogbomoso and Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria.

A sample of 5 mL of venous blood was collected from each participant into ethylenediaminetetraacetic acid (EDTA) bottle for laboratory investigations. Thick and thin blood films stained with 3% Giemsa were examined for detection of malaria parasite. Lysate of each sample was prepared by lysing 2 volumes of washed packed cells in 1 volume of carbon tetrachloride. The haemolysate of each sample was loaded on the cellulose acetate paper along with control samples. The 250-350 V was applied for 20 minutes or until visible and clear separation was obtained. ABO blood group antigens tests were performed by standard tile and tube techniques. Controls were set up appropriately. Commercially prepared anti-A and anti-B were used according to manufacturer's instruction.

Statistical Analysis

The statistical package for Social Sciences (SPSS version 14) was used for statistical analysis. Differences between percentages and proportions were tested by chi-square test. Means were compared using Student's t test. A p-value of < 0.05 was considered to be significant.

RESULTS

Altogether, 972 individuals participated in this study comprising 486 (50.3%) acute malaria subjects and 486 apparently healthy controls; 481 males and 491 females. Of the malaria subjects, 234 (48.1%) were men and 252 (51.9%) were women while there were 247 (50.8%) male and 239 (49.2%) female controls. The mean ages of test subjects (31.6±11.9 years) and controls (32.1±12.3 years) were not significantly different ($t = 0.644$, $p=0.91$).

Table1 shows that ABO blood groups distributions in the malaria and control groups were similar overall ($\chi^2 = 1.14$, $df = 3$, $p = 0.767$) and in both male ($\chi^2 = 2.137$, $df = 3$, $p = 0.544$) and female ($\chi^2 = 1.45$, $df = 3$, $p = 0.693$) groups. This implied that there was no significant association between ABO blood groups and occurrence of mild malaria.

Table 2 shows that haemoglobin variants distributions in the malaria and control groups varied significantly overall ($\chi^2 = 27.09$, $df = 5$, $p < 0.001$) and in both male ($\chi^2 = 10.793$, $df = 3$, $p = 0.013$) and female ($\chi^2 = 15.976$, $df = 3$, $p = 0.001$) groups. This implied that there was a significant association between haemoglobin variants and mild malaria. Haemoglobin AA individuals were significantly more infected than HbAS individuals ($\chi^2 = 13.533$, $df = 1$, $p < 0.001$) and HbAC individuals ($\chi^2 = 8.523$, $df = 1$, $p = 0.004$). There was no significant difference between HbAA individuals and: (i) HbSS individuals infected ($\chi^2 = 3.922$, $df = 1$, $p = 0.048$) (ii) HbSC individuals infected ($\chi^2 = 1.31$, $df = 1$, $p = 0.252$) (iii) HbCC individuals infected ($\chi^2 = 0$, $df=1$, $p = 0.776$). Haemoglobin AS individuals were significantly less infected than HbSS individuals ($\chi^2 = 10.075$, $df = 1$, $p = 0.002$) and Hb SC individuals ($\chi^2 = 4.932$, $df = 1$, $p = 0.026$) but not significantly different HbCC individuals infected (Yates $\chi^2 = 0.379$, $p = 0.538$). Similarly, HbAC individuals were significantly less infected than (i) HbSS individuals ($\chi^2 = 10.325$, $df = 1$, $p = 0.001$) and HbSC individuals ($\chi^2 = 5.507$, $df = 1$, $p = 0.019$) but not significantly different from HbCC individuals infected (Yates $\chi^2 = 0.620$, $p = 0.431$). There was no significant difference between HbAS and HbAC individuals infected ($\chi^2 = 0.303$, $df = 1$, $p = 0.582$).

Table 3 shows the distributions of ABO blood groups and haemoglobin variants in malaria (Mal) and control (Cont) groups. Group AB was excluded from this analysis due to its small number in the control group. While the distributions of A, B and O blood groups and haemoglobin variants in the malaria group varied significantly ($\chi^2 = 14.87$, $df = 6$, $p = 0.02$), the distribution of A, B and O and haemoglobin variants in the control group did not ($\chi^2 = 0.899$, $df = 6$, $p = 0.989$). This implied that there was a significant association between ABO blood groups and haemoglobin variants in the malaria group but not in the control group. Further Chi-square tests showed that the significant association observed among the ABO blood group distributions in the malaria group was between AA and AS variants only ($\chi^2 = 7.931$, $df = 2$, $p = 0.019$). Proportion of malaria infection increases as follows:

O+AS (0.345) < B+AS (0.424) < A+AS (0.468) < A+AA (0.489) < B+AA (0.55) < O+AA (0.568). Group O+AS individuals had the lowest number of malaria cases while group O+AA individuals had the highest number of malaria cases. Group O+AS individuals had significantly less malaria cases than (i) group A+AA individuals (χ^2 = 5.06, df = 1, p = 0.024) (ii) group B+AA individuals (χ^2 = 10.046, df = 1, p = 0.002) and (iii) group O+AA individuals (χ^2 = 16.998, df = 1, p < 0.001). Group B+AS individuals had significantly less malaria cases than group O+AA (χ^2 = 4.49, df = 1, p = 0.03).

Table 1: ABO Blood Groups Distribution in Malaria Subjects and Controls in Osogbo, Southwestern Nigeria

Blood group	All Subjects		Males		Females	
	Malaria(%)	Control(%)	Malaria(%)	Control(%)	Malaria(%)	Control(%)
O	230(47.3)	237(48.8)	110(47.0)	124(50.2)	120(47.6)	113(47.3)
A	115(23.7)	119(24.5)	54(23.1)	55(22.3)	61(24.2)	49(20.5)
B	117(24.1)	112(23.0)	55(23.5)	59(23.9)	62(24.6)	68(28.4)
AB	24 (4.9)	18(3.7)	15(6.4)	9 (3.6)	9(3.6)	9(3.8)
TOTAL	486	486	234	247	252	239

Table 2: Haemoglobin Variants Distribution in Malaria Subjects and Controls in Osogbo, Southwestern Nigeria

Blood genotype	All Subjects		Males		Females	
	Malaria(%)	Control(%)	Malaria(%)	Control(%)	Malaria(%)	Control(%)
AA	321(66.0)	270(55.6)	156(66.7)	145(58.7)	165(65.5)	125(52.3)
AS	102(21.0)	150(30.9)	48(20.5)	72(29.2)	54(21.4)	78(32.6)
AC	30(6.2)	51(10.5)	15(6.4)	24(9.7)	15(6.0)	27(11.3)
SS	16(3.3)	5(1.0)	7(3.0)	3(1.2)	9(3.6)	2(0.8)
SC	11(2.3)	5(1.0)	6(2.6)	1(0.4)	5(2.0)	4(1.7)
CC	6 (1.2)	5(1.0)	2(0.9)	2(0.8)	4(1.6)	3(1.3)
TOTAL	486	486	234	247	252	239

Table 3: Distributions of ABO blood groups and Haemoglobin variants in Malaria Subjects and Controls in Osogbo, Southwestern Nigeria

Blood group	AA Malaria/Control	AS Malaria/Control	AC Malaria/Control	SS/SC/CC Malaria/Control	Total Malaria/Control
O	172/133	38/72	11/25	9/7	230/237
A	65/68	30/34	8/13	12/4	115/119
B	72/59	28/38	8/12	9/3	117/112
AB	12/10	6/6	3/1	3/1	24/18
TOTAL	321/270	102/150	30/51	33/15	486/486

DISCUSSION

In this study, the distributions of ABO blood groups in the test and control subjects were similar. These distributions were consistent with those of previous reports of ABO studies in the study area (Falusi *et al.,* 2000; Igbeneghu *et al.,* 2012; 2014). The present study showed that mild malaria infection prevalence was not dependent on ABO blood groups. Some previous studies had demonstrated lack of association between ABO blood group and prevalence of mild malaria (Degarege *et al.,* 2012 Igbeneghu *et al.,* 2014). However, Agbonlahor et al. (1993) and Nkon-Akenji *et al.* (2004) reported that blood groups O and B were the most and the least susceptible to mild malaria respectively. These contrasting reports might be suggestive of the fact that there other genetic factors that play some more significant role with regard to prevalence of acute malaria than the ABO blood groups.

In this study, the distributions of haemoglobin variants in the test and control subjects were at variance. The prevalence of uncomplicated malaria varied significantly with haemoglobin variants. Haemoglobins AS and AC protected against malaria infection. A number of previous studies had reported protection of HbAS against mild malaria (Williams *et al.,* 2005; Igbeneghu *et al.,* 2015). Similarly, some studies had suggested protective effect for HbAC against mild malaria (Modiano *et al.,* 2001; Rihet *et al.,* 2004; Igbeneghu *et al.,* 2015). Individuals with HbSS are known to often develop potentially lethal sickle-cell anaemia and so are not protected against malaria but HbCC only results in mild clinical phenotype and reports have shown that it protects against malaria (Modiano *et al*., 2001). Several mechanisms had been suggested for protective effects experienced by HbAS and HbAC individuals including impaired entry into and growth of parasites in red cells (Cooke and Hill, 2001; Weatherall and Clegg, 2001; Rihet *et al.,* 2004).

When the combined effect of ABO blood groups and Haemoglobin variants were considered, we observed that there were significant associations between ABO blood groups and haemoglobin variants with respect to malaria infection. Group O individuals who were AS were least infected with malaria while group O individuals who were AA were most infected. Where AA individuals predominate, blood groups A and B individuals are likely to be less infected compared to group O while where AS individuals predominate, group O individuals are likely to be less infected compared to groups A and B. This could be the reason why there are contrasting reports on the relationship between ABO and malaria infection. From this study, it is not correct to associate highest malaria infection with blood group O alone. In fact, O+AS individuals were the least infected while O+AA were the most infected and this signified that prevalence of malaria infection is actually dependent on haemoglobin genotype.

ACKNOWLEDGEMENTS

We thank the volunteers who participated in this study. Also, we are grateful to the Management and Staff of Ladoke Akintola University Teaching Hospital and Osun State General Hospital, both in Osogbo, Osun State for their co-operation during the course of this study.

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10/8/2022